

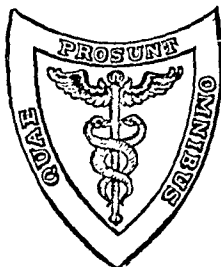
THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.
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NEW SERIES

VOL. 204



LEA & FEBIGER
PHILADELPHIA

1942

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1942

PRINTED IN U. S. A.

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THE
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JULY, 1942

ORIGINAL ARTICLES.

**THE LIFE-SAVING POWER OF "SAFE" UNIVERSAL DONOR
BLOOD IN EXSANGUINATING HEMORRHAGE.**

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IN 1935, Marriott and Kekwick^{3a,b} pointed out that the routine procedure of giving 500 cc. of blood at each transfusion to adults was often inadequate in severe anemias and in bleeding cases. They have performed 194 transfusions of citrated blood by the drip method, administering an average of between 2 and 4 liters of blood per case. One of their patients received as much as 5650 cc. of blood within a 48-hour period. These workers did not restrict themselves to the use of donors of the homologous group but also used donors of other groups according to the universal donor principle. They apparently relied on the slow rate of infusion which allowed time for the body to dispose of the foreign isoagglutinins.

The use of universal donor blood for patients not belonging to Group O is usually regarded as unsafe when the isoagglutinins in the donor's serum are of high titer.² Though the slow infusion of such blood is probably harmless, if the blood is injected rapidly over a short period of time, particularly to a severely anemic patient, hemolysis of the patient's own blood cells could conceivably occur. Indeed, a number of reports of hemolytic reactions following the use of universal donor's blood have appeared, which have been

attributed to this mechanism.^{1,4} Witebsky, Klendshoj and Swanson^{6,7} have advocated the routine addition to the citrated Group O donor's blood of a solution of purified A and B substances in order to neutralize the isoagglutinins and make the blood safe for patients of all groups.

Case Report. A man, aged 65, while under observation at the hospital for peptic ulcer, suddenly went into shock; his blood pressure dropped to 50/30, his pulse being almost imperceptible, his skin cold and clammy, and he passed a large amount of blood by rectum.

The patient was typed as Group AB, and transfusions totaling 1190 cc. of citrated blood from two compatible AB donors were given. Within 5 hours the patient reacted and his blood pressure rose to 108/76. During the night, however, he had another large hemorrhage and in the morning was again in shock. A transfusion was started at once. Operation by Dr. Louis Berger, revealed a penetrating duodenal ulcer at the base of which was the eroded and bleeding pancreatico-duodenal artery. The bleeding from the eroded vessel was controlled and a subtotal gastrectomy was performed.

During the procedure the transfusion of citrated blood was continued, the blood being allowed to run in rather rapidly. When 2000 cc. of blood, in addition to the 1100 cc. given on the previous day, had been transfused, no more Group AB donors could be obtained. Accordingly, additional blood was taken from Group O donors, 10 cc. of Witebsky's solution of purified Group A and B substance* being added to each 500 cc. of blood. In this manner 2000 cc. of universal donor blood were transfused. The patient responded to the transfusions only after the bleeding vessel had been located and ligated by Dr. Berger. By the time the procedure was completed, the patient had received a total of more than 5000 cc. of blood.

Immediately after the operation, the patient's blood pressure was 150/90, pulse rate 100 and of good quality; his skin was dry and warm and his general condition good. He improved slowly after the operation but in general his convalescence was uneventful.

Comment. As a precaution the isoagglutinins in the blood from 4 Group O donors, used for transfusing a Group AB patient, were neutralized by adding a solution of purified A and B substances as recommended by Witebsky, Klendshoj and Swanson. Whether or not harm would have resulted if this procedure had not been followed cannot be determined, but the efficiency of the group substances in neutralizing the isoagglutinins has been demonstrated by titration tests *in vitro*, (cf. Table I) which indicate at least that this procedure eliminates a theoretical danger. The group substances have been used in transfusions by Witebsky *et al.*, in more than 100 cases, and by the present authors in about 20 cases without the occurrence of

only 88% while on admission it had been 100%, and this despite the transfusion of more than 5 liters of blood, indicates that he lost at least as much blood as he received. In fact, the patient must have been almost completely exsanguinated, and there can be no doubt that without the transfusions he could not have survived the operative procedure.

TABLE 1.—EFFECT OF ADDITION TO GROUP O DONOR'S CITRATED BLOOD OF A SOLUTION OF A AND B GROUP SUBSTANCES ON THE TITERS OF THE ISOAGGLUTININS IN THE PLASMA.

Donor's plasma.	Tested against cells.	Dilutions of plasma.							
		Undil.	1:2.	1:4.	1:8.	1:16.	1:32.	1:64.	1:128.
Before addition of group substance	A ₁	++	+++	+++	+++	++	+	tr.	—
	B Rabbit	++ hem.	++ +++	++ ++	++ ++	++ ++	tr. +	— tr.	— —
After addition of group substance	A ₁	±	tr.	—	—	—	—	—	—
	B Rabbit	+++	++	++	±	±	—	—	—

One drop each of plasma or plasma dilution and test cells (2% suspension in terms of blood sediment) were mixed in small test tubes. Readings were taken after 1 hour.

Note that while the anti-A and anti-B isoagglutinins are neutralized by the group substances, the titer of the agglutinins for rabbit cells is only slightly reduced. This demonstrates the specificity of the reactions.

It should be noted that the transfusion of plasma alone in our case would undoubtedly have been inadequate to maintain life on account of the vast amount of blood lost. While in smaller hemorrhages the loss of red cells is not serious and satisfactory results can be obtained by merely restoring the blood volume with transfusion of plasma, in larger hemorrhages replacement of at least part of the lost erythrocytes is essential. In emergencies when whole blood is not available or is available only in small amounts, plasma is of great value and certainly far superior to glucose and saline infusions; but if the hemorrhage continues, it is recommended that at least one transfusion of whole blood be given for every 2 or 3 transfusions of plasma. In this connection the transfusion of outdated bank blood, *e. g.*, blood stored in citrate without glucose for more than 2 weeks, would have resulted in only temporary benefit to our patient since the erythrocytes of such blood are rapidly broken down and eliminated from the circulation within a few hours or days.⁵

Summary. A patient almost completely exsanguinated by bleeding from a duodenal ulcer, was operated on and the vessel ligated. Preoperatively and during the operation (all within a period of less than 24 hours) the patient, who belongs to Group AB, received transfusions totaling well over 5000 cc. of blood from 10 blood donors. Six of the donors used belonged to Group AB, 4 to Group O. To the blood of the latter a purified solution of group substances was added to neutralize the isoagglutinins. Clinical recovery followed in a situation in which customary transfusion procedures would undoubtedly have been inadequate.

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GELATIN AS A SUBSTITUTE FOR BLOOD AFTER EXPERIMENTAL HEMORRHAGE.*

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THE possibility that solutions of gelatin might be used to restore the volume of circulating fluid, has occurred to a number of investigators.^{4,9,11} Recently, increased interest in blood substitutes has led to a more detailed study¹⁰ of certain types of gelatin. Transfusions of solutions of isinglass, made from the swim-bladders of fish, have been shown to insure the survival of dogs after massive hemorrhage which otherwise would be likely to end fatally.⁹ Gelatin made from calfskin has been shown to be even more effective than isinglass for this purpose, to remain in the circulation in detectable concentration for at least 24 hours, and to be non-toxic and non-antigenic for dogs and rabbits.¹⁰ Since gelatin, even of the highest grade, is not a pure substance, but a mixture, it is subject to considerable variation when prepared in different plants, and even when prepared in the same plant at different times. It seemed desirable, therefore, to repeat some of the older experiments, using a specially prepared gelatin. The gelatin selected was prepared by hydrolysis of alkali-treated bone collagen, and was supplied as calcium gelatin.⁴ The danger of contamination with pathogenic spores, as suggested by some workers,⁹ is probably less with gelatin prepared from bone than with gelatin prepared from hides.

It is well known that even crystalloidal injections may temporarily restore the volume of the circulation¹ and, by permitting an animal

to mobilize its plasma proteins, allow survival of an otherwise fatal hemorrhage. For this reason, the observation that the injection of a solution causes animals to survive massive hemorrhage offers no basis for judging its relative effectiveness as a blood substitute. The experiments reported here were planned to provide a *direct* comparison between gelatin and a crystalloidal solution, and between gelatin and defibrinated blood.

Materials, Methods, and Results. Four samples, obtained at different times, of each of two types of gelatin, were studied. The average molecular weight of Type 1 was reported as being higher than that of Type 2. An 8% solution of No. 1 and a 10% solution of No. 2, in 0.9% sodium chloride, were found to be sufficiently fluid, when warmed to body temperature, to pass through a 21-gauge needle. These solutions were autoclaved at 15 pounds pressure for 20 minutes, and stored in sterile containers at 4° C. All solutions were cultured aerobically and anaerobically. No growth has been obtained in any of the 35 solutions which have been prepared during the course of this study. Solution 1, after autoclaving, had specific gravity 1.2, pH 5.93, and colloidal osmotic pressure (in collodion bag against 0.9% sodium chloride) 8.5 mm. Hg. Solution 2 had specific gravity 1.25, pH 6.0, and colloidal osmotic pressure 14.5 mm. Hg.

A preliminary study of the toxicity of the autoclaved gelatin solutions was done on a series of 7 dogs. In none of these was a change in arterial pressure or respiration obtained on injection of as much as 20 cc./kg. of either type of gelatin, at an injection rate of approximately 3 cc./kg./min. The effect of excessively large doses (up to 90 cc./kg.) was studied by withdrawing blood in equal volume as the gelatin solution was injected. Even in these doses no depressor agents could be demonstrated. Confirmatory data were obtained in the course of the studies reported below, in which arterial pressure lowered by previous hemorrhage underwent steady elevation to approximately its prehemorrhage level as gelatin solution was injected. The latter studies have been extended to include a total of 8 samples of gelatin and a total of 45 dogs, without obtaining evidence for toxicity in any case.

Antigenicity of the autoclaved solutions of gelatin was studied in 2 dogs. After receiving 40 cc./kg. of gelatin solution in replacement of blood lost by hemorrhage, they were permitted to recover. Nine and 11 weeks later, respectively, they were etherized and injected with 40 cc./kg. of the original solution, without effect on arterial pressure or respiration.

Postmortem examination was done on all the animals used in the toxicity studies, including the 2 animals which were permitted to survive. In no case was evidence of thrombosis, hemolysis, embolism, or capillary damage found. Necropsies were also done on some of the animals used in other portions of the study, without revealing pathologic changes.

Since neither type of gelatin appeared to be toxic for the dog, and since the data offer no clear-cut evidence that they differ in effectiveness as circulating fluid, the data on the two types are treated collectively in the following.

A comparison of the solutions studied (8 or 10% gelatin in 0.9% NaCl, 5% glucose in 0.9% NaCl, and defibrinated blood) was obtained by determining, in dogs under ether anesthesia: (a) the percentage restoration of carotid arterial pressure (Hg manometer, kymograph records) following a massive standard hemorrhage, on replacing the blood lost with an equal volume of one of the three solutions; (b) the permanence of the restoration of arterial pressure following *a* up to 2 hours; (c) the ability of the animals, after procedures *a* and *b*, to withstand a second hemorrhage. The pro-

cedures for withdrawing blood and injecting solutions were made as nearly standard as possible, particularly with respect to the rate of the hemorrhage or injection, and the time elapsing between the end of the hemorrhage and the beginning of the injection.

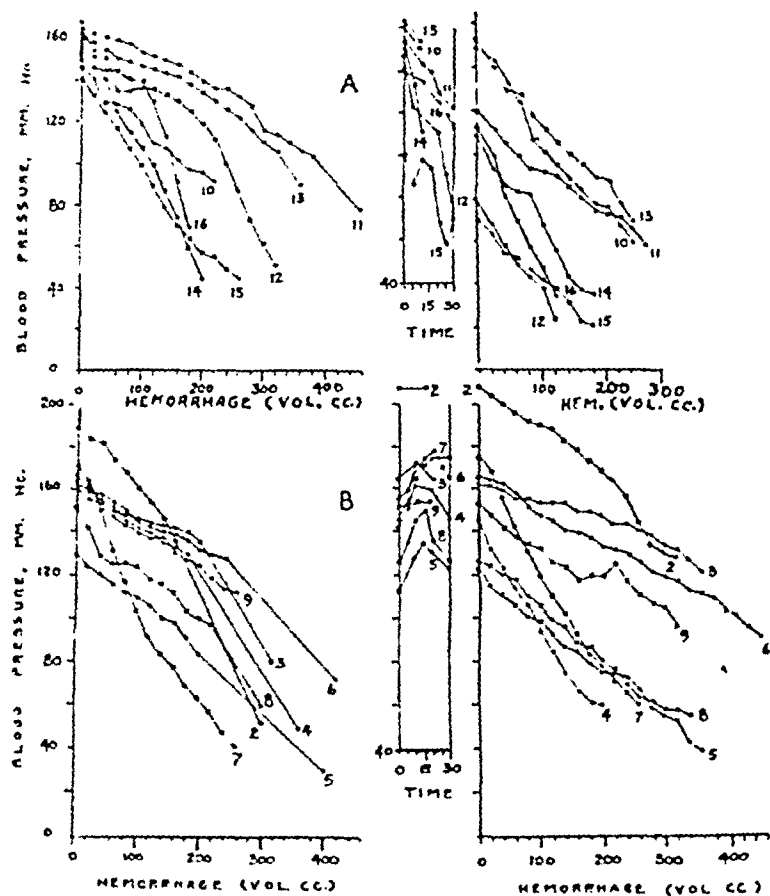


CHART 1.—Comparison of 5% glucose in 0.9% NaCl (A) with 8% to 10% gelatin in 0.9% NaCl (B). In both A and B, the curves on the left show the relationship in individual dogs (numbered on the curves) of arterial pressure to the volume of blood drawn in progressive hemorrhage (see text). The middle set of curves shows the change in arterial pressure with time following injection of either glucose-saline (A) or gelatin-saline (B). Time is given in minutes following completion of the injection. The curves on the right show the relationship of arterial pressure to the volume of blood drawn during second hemorrhage, begun in each case at the time indicated by termination of the preceding time record.

approximately 3 cc./kg. per minute. As is shown in the figure, the immediate restoration caused by the two solutions was not strikingly different. Following the injection, however, every animal receiving the crystalloidal solution showed a considerable fall in pressure (Chart 1A). In contrast, all the animals receiving gelatin (Chart 1B) showed a rise above the immediate postinjection level, usually reaching a peak within 10 to 15 minutes; and in no case was arterial pressure lower, at the end of 30 minutes, than immediately following the injection. Chart 1 also shows the difference in the ability of the two groups of animals to maintain arterial pressure during the second hemorrhage, performed in the same manner as the first and beginning up to 30 minutes after the injection. The animals receiving gelatin to replace the blood lost during the first hemorrhage, appeared to be as capable of maintaining arterial pressure during the second hemorrhage, as they had been originally (Chart 1B). On the other hand, those receiving glucose-saline invariably showed a greater fall in pressure for a given volume of hemorrhage, than originally (Chart 1A).

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA.

Dog No.	Wt. (kilo).	Control B.P. (mm. Hg).	Initial hemorrhage.				B.P. after replacement.				Second hemorrhage.	
			Vol. cc. A.	B.P. at end.		Immediate.		30 min. later.		Vol. cc. B.	Ratio, vol. B: vol. A.	
				Mm. Hg.	%	Mm. Hg.	%	Mm. Hg.	%			
					control.		control.		control.			control.
GLUCOSE-SALINE.												
10	8.0	146	280	80	54.8	160	109.6	140	0.5 : 1	
11	12.6	162	440	76	46.9	152	93.8	120	74.0	220	0.5 : 1	
12	9.1	164	320	50	30.5	148	90.2	78	47.6	80	0.25 : 1	
13	10.3	160	360	86	53.8	162	101.2	200	0.55 : 1	
14	5.9	166	200	44	26.5	150	90.3	140	0.7 : 1	
15	7.4	140	260	44	31.4	100	71.4	70	50.0	120	0.46 : 1	
16	5.2	150	180	68	45.3	144	96.0	112	74.7	80	0.44 : 1	
Avg.	8.3	155.4	291	64	41.3	145	93.2	95	61.6	143	0.49 : 1	
GELATIN-SALINE.												
2	8.6	190	300	58	30.5	208	109.9	260	0.87 : 1	
3	9.1	160	320	90	56.2	166	103.7	360	1.12 : 1	
4	10.3	166	360	50	30.1	148	89.1	146	88.0	180	0.5 : 1	
5	11.8	130	400	30	23.0	114	87.7	124	95.4	200	0.5 : 1	
6	12.0	162	420	86	53.1	154	95.0	166	102.4	500	1.19 : 1	
7	7.4	172	260	40	23.2	142	82.5	176	102.3	260	1.0 : 1	
8	8.6	148	300	68	46.0	128	86.5	126	85.1	240	0.8 : 1	
9	7.4	164	260	116	70.7	156	95.1	240	0.92 : 1	
Avg.	9.4	161.5	327.5	67.2	41.6	152	93.7	147.3	94.6	280	0.86 : 1	

Table 1 summarizes the pertinent data of Chart 1, as a basis for a quantitative comparison of the two solutions. As is shown in the table, in both groups the average volume of blood drawn during the initial hemorrhage amounted to approximately 40% of the animal's estimated blood volume (calculated as 8% of body weight). Arterial pressure at the end of this type of hemorrhage averaged 41.4% of the control. Although the immediate restoration of arterial pressure was nearly complete and equal with the two solutions, after a lapse of 30 minutes, pressure in the glucose-saline group had fallen to 61.6% of the control, while in the gelatin group it was still at 94.6% of the control. The last two columns in the table show the volume of blood which had to be drawn during the second hemorrhage in order to approximate the arterial pressure reached after the first hemorrhage, and the ratio of this volume to the volume of the initial hemorrhage. For the glucose-saline group, the ratio of the volume of the second hemorrhage, to that of the first (both resulting in lowering the blood pressure to approximately equal levels) was 0.49:1; for the gelatin group, the ratio

averaged 0.86:1. On the basis of these criteria, the relative ability of gelatin and glucose-saline solutions to replace blood as circulating fluid for a period of 30 minutes, may be arbitrarily expressed as the ratio 86:49.

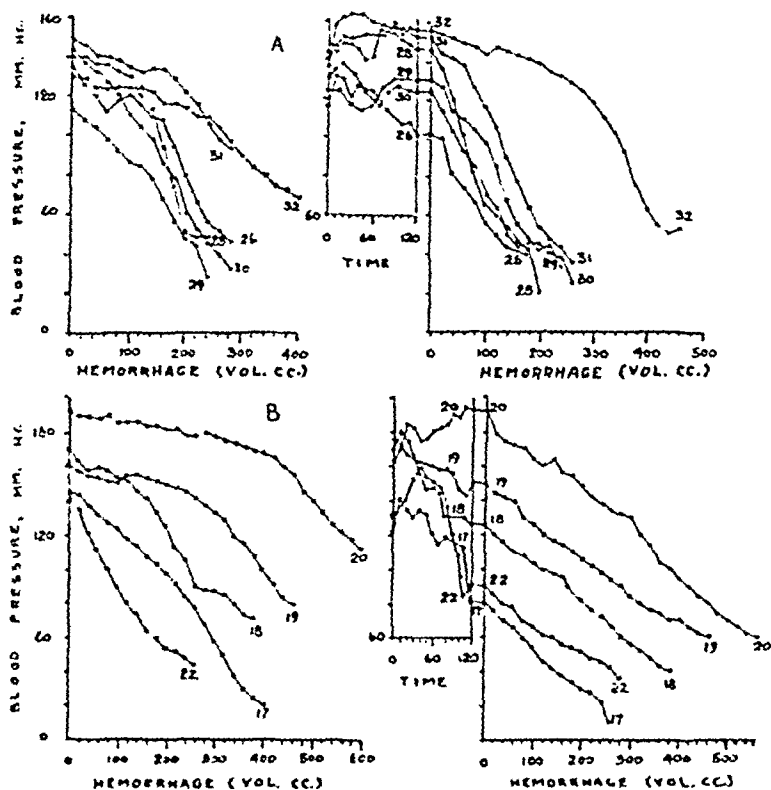


CHART 2.—Comparison of defibrinated blood (A) with 8% to 10% gelatin in 0.9% NaCl (B). Construction of figure exactly as in Chart 1.

A comparison of gelatin with defibrinated blood is shown in Chart 2. The experiments were carried out in the same manner as those described above, except that arterial pressure was followed for 2 hours after the initial hemorrhage and injection. As is shown in Chart 2B there was usually no fall in pressure below the immediate postinjection level for the first hour in the dogs receiving gelatin. There was usually, however, considerable lowering of pressure during the second hour (the average lowering during the entire 2-hour interval is 14% of the immediate postinjection pressure). The animals receiving defibrinated blood (Chart 2A) serve as a control, for all the experiments reported here, on the effects of the anesthesia and on the effect of the temporary reduction of blood volume during the first hemorrhage, with optimum replacement. As is shown in this Chart, these animals as a rule maintained a fairly constant arterial pressure throughout the period of observation following restoration of the blood volume lost during the initial hemorrhage. They also showed only a slight loss of ability to maintain pressure during the second hemorrhage. The dogs receiving gelatin started the second hemorrhage with a lower pressure than did those receiving blood, but as a rule showed a more gradual reduction in pressure as the hemorrhage progressed, a phenomenon deserving of further study.

Discussion. The ability of the cardiovascular system to maintain arterial pressure during severe hemorrhage is probably as rigorous a test as can be applied to the system. An interpretation of such a test in terms of the separate factors which govern arterial pressure, such as blood volume, blood viscosity, the work of the heart, tone of arterioles, and so on, is obviously impossible⁸ without additional data. It appears, however, to offer certain advantages, in addition to its simplicity, in an investigation of this sort, where interest centers primarily about the ability of the circulation to keep itself going, and where the mechanism which enables it to do so is of secondary concern. On the basis of such a test, gelatin appears to be definitely superior as a blood substitute to glucose-saline, although, as might be expected, it is inferior to defibrinated blood. This conclusion is supported by the other data presented here, which show that gelatin solutions restore arterial pressure after it has been lowered by hemorrhage, for a considerably longer time than does glucose-saline. Again, in this respect, gelatin solutions appear to be inferior to defibrinated blood. That the elevation of arterial pressure produced by the gelatin is not due merely to its effect in increasing blood viscosity^{2,6} is suggested by the fact that pressure continues to rise for 10 to 15 minutes after the injection, as it does after injecting defibrinated blood. Such a postinjection rise would be expected if the injection increased the colloidal osmotic pressure of blood, and so permitted blood volume to increase for a time after the injection was completed. Obviously, this interpretation cannot be given with assurance without data on blood volume.

A clinical study of the effect of intravenous injection of these gelatin solutions in human subjects is now in progress.⁷ The results thus far obtained have been encouraging, since no severe reactions have followed transfusion with our solutions. It appears that gelatin from this particular source, prepared according to the directions given here, is without immediate toxicity for the human as well as for the dog. One of the early objections to gelatin for intravenous use, namely, that heating it to sterilizing temperatures would cause toxic decomposition,¹ does not seem to be applicable to the gelatin which we studied. In view of possible variation in gelatin even from the same source, test solutions are prepared from each new batch, autoclaved, cultured, and tested on the dog for toxicity.

The question of antigenicity for the human cannot be answered from our data on the dog, or the data of others.^{9,10} Although gelatin is usually regarded as non-antigenic, the possibility of antigenic contaminants cannot be dismissed lightly when dealing with such an impure substance. A thorough investigation of this question is planned.

A final clinical evaluation of gelatin solution as a blood or plasma substitute will have to be postponed until the question of antigenicity for the human is settled. It cannot be predicted with

assurance whether gelatin will show any superiority over crystalloidal solutions in a vascular system damaged by shock, since our comparative data were obtained by study of a system which is normal except for the effects of anesthesia.

Since this study was begun, a number of publications have appeared on purified bovine albumin as a substitute plasma colloid.² Although the available data show that this material is non-toxic and capable of maintaining the circulation, data on its antigenicity for the human are lacking. Occasional subjects are reported as giving positive reactions to intradermal injection.³ Since the determination of antigenicity for materials injected intravenously is largely on an empirical basis, data on this point will accumulate slowly. In view of the urgency of the present need for transfusion fluids it would be premature, therefore, to discontinue study of other blood substitutes.

Summary. Etherized dogs were subjected to massive hemorrhage under controlled conditions, and the volume of blood drawn was replaced immediately with defibrinated blood, with a heat-sterilized solution of bone gelatin 8 to 10% in 0.9% NaCl, or with 5% glucose in 0.9% NaCl.

All three of these solutions produced practically complete immediate recovery of arterial pressure. The restoration of pressure with defibrinated blood was still practically complete at the end of 2 hours. The restoration with gelatin was usually still complete at the end of the first hour, and approximately 86% complete at the end of the second hour. The restoration with glucose-saline was only 62% complete at the end of 30 minutes. The dogs restored with gelatin suffered no greater fall in pressure during second hemorrhage than did the dogs restored with defibrinated blood. The dogs restored with glucose-saline, however, were less able to withstand second hemorrhage than those of the other two groups.

No effects on arterial pressure or respiration suggesting the presence of toxic proteoses or amines in these autoclaved gelatin solutions were observed in dogs receiving up to 20 cc. kg. without previous hemorrhage (7 dogs) or in dogs receiving up to 90 cc. kg. after hemorrhage (38 dogs). Anaphylactoid reactions were not observed in animals (2 dogs) injected with 40 cc. kg. of gelatin solution 9 to 11 weeks after a sensitizing injection of 40 cc. kg. No pathologic changes were demonstrable on necropsy in any of the animals used in this study, including the two latter animals.

Conclusions. Gelatin solutions appear to occupy an intermediate position between blood and crystalloidal solutions in their ability to maintain the circulation after blood loss. The restoration of the circulation by gelatin lasts sufficiently long to cover many clinical emergencies. Since the samples of gelatin which have been tested can be made up in solution and autoclaved to sterility without the development of demonstrable toxicity for the dog, further study with a view to clinical trial is indicated.

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STUDIES ON THE HEMORRHAGIC AGENT, 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN).

II. THE METHOD OF ADMINISTRATION AND DOSAGE.*

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IN 1939 Prof. Karl Paul Link^{2,3,5,9} and his associates isolated and crystallized the active principle in spoiled sweet clover that was responsible for the hemorrhagic disease of cattle. Shortly thereafter a series of brilliant investigations culminated in the synthesis of a compound that was identical in biologic characteristics to the isolated principle. This substance is 3,3'-methylenebis (4-hydroxycoumarin).†

In a previous report¹ it was demonstrated that the administration of this dicoumarin either orally, or intravenously in the form of the disodium salt, is succeeded by protracted prolongation of the prothrombin time and coagulation time in dogs and human beings. This effect follows an initial latent period of 24 hours or more succeeding the exhibition of the material. No untoward symptoms attended the administration of this substance in therapeutic amounts, but excessive quantities produced spontaneous hemorrhages and fatalities in dogs. Postmortem examination with gross and microscopic studies did not reveal significant pathologic change

* This study was aided in part by a grant from the Wisconsin Alumni Research Foundation.

† Hereafter in this paper this specific substance frequently will be referred to as dicoumarin for the sake of simplicity, even though other dicoumarin derivatives are under investigation.

in the liver or kidneys; but it did show, in many animals, widespread dilatation of capillaries, arterioles, and venules. No lesions in the walls of the vessels were observed. At the time of the original communication the potential hazards of this dicoumarin and its possible advantages over heparin were discussed.

When the previous report was published, 3,3'-methylenebis (4-hydroxycoumarin) had been given to only 22 patients. The first 16 had received small doses, 2 mg. per kilo or less, and the results were either negligible or very moderate. In the remaining 6, the effects were striking. Since July, 1941, the substance has been given to 51 patients of varying ages, of both sexes, and under a wide variety of clinical conditions. Thus to date we have administered the material to 73 patients. This communication reports the results of administering this dicoumarin to human beings and suggests the proper dosage.

Methods. The prothrombin time was determined on undiluted plasma with Pohle and Stewart's modification⁶ of Quick's method. On each day that tests were made 1 or more untreated patients were tested; these served as a control for check upon the technique and potency of the thromboplastin. Ordinarily the thromboplastin was of such potency that the normal prothrombin time for human beings was 9.5 to 10.5 seconds. The approximate percentages of prothrombin in human plasma as derived from the chart of Pohle and Stewart are as follows: a time of 12.5 seconds indicates a concentration of about 50% of normal; 19 seconds, 25% of normal; and 30 seconds, 12.5% of normal. A time longer than 45 seconds was generally less accurate because of the greater difficulty in determining the end point.

The coagulation time was measured at room temperature by the 2-tube method of Lee and White. Great care was taken to make sharp venipunctures, to have a free flow of blood, to avoid too great suction in the collection of samples, to avoid air bubbles, and to transfer the blood to the test tubes with a minimum of agitation. The tubes were scrupulously clean and the syringe clean and wet. By this method the normal coagulation time ranges from 6 to 12 minutes.

Materials. 3,3'-Methylenebis (4-hydroxycoumarin) was used exclusively in oral administration experiments; the disodium salt of this substance, which was in concentration of 10 mg. per cc. and at a pH of 10, or slightly higher, was the only material used intravenously. These materials were furnished us through the kindness of Professor Link and Dr. Stahmann.

Patients. The patients had a wide variety of diseases. The object of administering the dicoumarin was to establish a proper and safe dosage rather than to test the therapeutic efficacy of the substance. Six of the patients had thrombosis, but in the rest there was no such indication for the drug. Many of the patients, particularly those studied earlier, were in advanced stages of a malignant disease. Both sexes were represented, ranging in age from 10 to 73 years.

Complete blood counts, urine analyses, blood sugar and non-protein nitrogen determinations, and the Rumpel-Leede tourniquet test were done in all cases. In many, but not all, the hippuric acid liver function test, the cephalin-cholesterol flocculation test,⁴ the icterus index, the bleeding time, and phenylsulphophthalalein renal function test were done before and after completion of observation. In a few, platelet counts were made. In no instance were there significant quantitative changes in the tests, neither

was there evidence that the hepatic or renal function was impaired as a result of the administration of the dicoumarin. In a few patients the control tests of hepatic function indicated the existence of liver damage. In these instances particular caution was exercised during and after the administration of the dicoumarin.

Results. Intravenous Administration. The disodium salt of 3,3'-methylenebis (4-hydroxycoumarin) has been given intravenously in varying doses to 27 patients. Of these, 24 received only 1 dose, 3 received repeated (2 to 5) doses. The single doses ranged from 0.5 mg. per kilo in 2 patients to 6 mg. per kilo in 1; the majority (15) received 4 mg. per kilo. The 3 patients who had repeated doses were given 4 mg. per kilo each time. The smallest doses

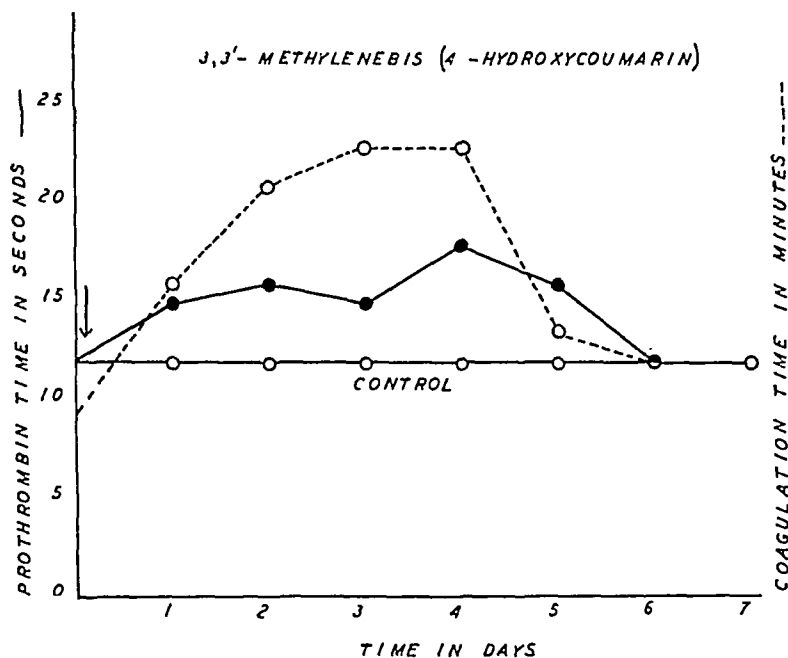


CHART 1.—Effect of an intravenous dose (4 mg. per kilo) of dicoumarin upon the prothrombin time and coagulation time of a 70-kg. white male. The control line indicates the prothrombin time in an untreated patient.

produced relatively little or no effect; the most effective single or repeated dose seemed to be about 4 mg. per kilo. The patients did not all respond identically to a given dose. In all cases, without regard to size of dose, there was a latent period of about 24 hours before a demonstrable effect took place. After one dose there was a usual period of from 2 to 5 days before the maximal effect was noted, after which there was a gradual return, over a period of 3 to 5 days, of the prothrombin time and coagulation time to normal. The effects of a single intravenous dose are shown in Chart 1 and the effects of repeated intravenous administration of the dicoumarin are shown in Chart 2. This route of administration was studied to determine the latent period and to rule out the variable factor of

absorption. It appeared to have no significant advantage over the oral administration in those cases that are able to take medication by mouth.

Oral Administration. 3,3'-Methylenebis (4-hydroxycoumarin) has been given orally to 46 patients in single or repeated doses, varying from 0.75 mg. per kilo to 6 mg. per kilo. In early studies most of the patients received single and small doses. As we became more familiar with the effects of the drug, larger and repeated doses were given. For a time it was customary to give repeated large doses orally every 3 to 6 days, but in recent months it has been the rule to give an original large dose and subsequent daily small doses,

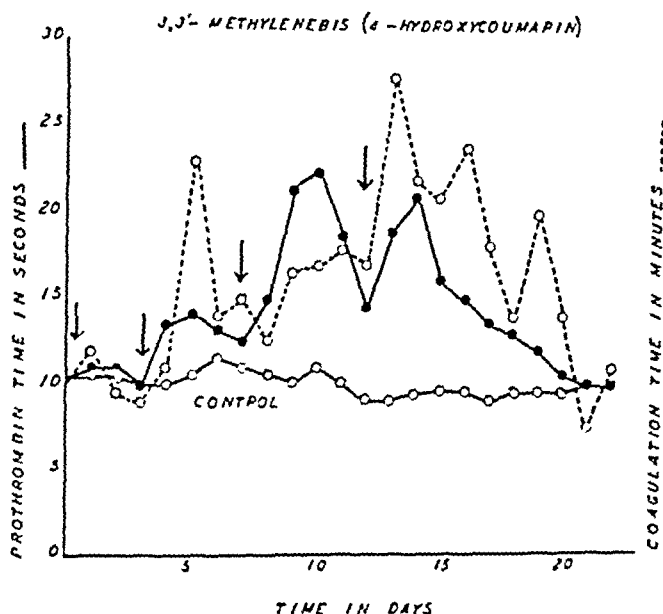


CHART 2. - Effect of 4 intravenous doses (4 mg. per kilo) of dicoumarin on the prothrombin time and coagulation time of a 65-kg. white male.

since this seemed to be the best method of maintaining a more uniform prolongation of prothrombin time and coagulation time. Typical responses to a large dose followed by daily small doses and to repeated large doses are shown in Charts 3 and 4.

The latent period, more prolonged, and the protracted effect upon the prothrombin time and coagulation time is demonstrated here as in the experiments where the drug was administered intravenously.

At present it is customary to give an initial dose of 5 mg. per kilo and to follow it with daily doses of 1.5 mg. per kilo. This dose is nearly always effective. The response to this dose varied considerably. In some patients the prolongation in prothrombin time and coagulation time was greater than was desired. When this occurred,

the material was withheld for 1 or more days, until there was a trend toward normal. It is imperative when using this anticoagulant to make daily determinations of the prothrombin and the coagulation time.

It was found that an initial dose of 5 mg. per kilo followed by daily doses of 1 mg. per kilo produced a satisfactory response in 5 of 16 patients. With an initial dose of 5 mg. per kilo, followed by daily doses of 1.5 mg. per kilo, however, satisfactory response was noted in 11 of 14 patients; the results are shown in Table 1.

3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN)

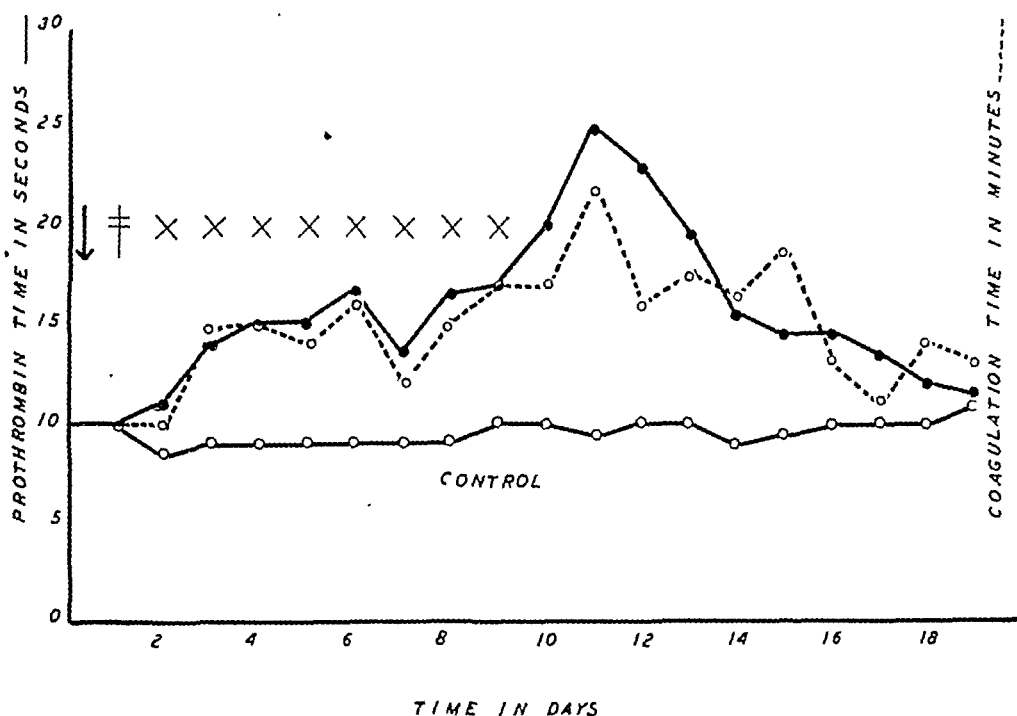


CHART 3.—Effect of repeated oral doses of dicoumarin on the prothrombin time and coagulation time of a 66-kg. white male. ↓ indicates a dose of 5 mg. per kilo. ‡ a dose of 1.5 mg. per kilo and × a dose of 1 mg. per kilo.

The prolongation in the prothrombin and coagulation time in the patients represented in the table is significant in all but 3 instances. In Cases 1, 2, 3, 4, and 8 the prolongation in coagulation and prothrombin time was greater than is theoretically necessary and actually reached hazardous levels. Although microscopic blood was noted in the urine or feces of 6 of these 14 patients, when coagulability of the blood was least, gross hemorrhage occurred in only 1 patient (a recently studied case). This was protracted and severe enough to cause real concern, and hence some details are warranted here.

CASE 1.—Mrs. H. V. B., a 44-year-old housewife who weighed 237 pounds (108 kilo), had chronic endocervicitis. Preliminary studies, including bleeding and coagulation time, the Rumpel-Leede test, blood non-protein

TABLE I—THE EFFECT OF ORAL ADMINISTRATION OF 3,3'-METHYLENES (1-HYDROXYCUMARINS) UPON THE COAGULATION AND PROTHROMBIN TIME. Original Dose of 5 Mg. per Kilo and Subsequent Daily Doses of 1.5 Mg. per Kilo.

No.	Sex	Prof.	Diagnosis	Age	Sex	Wt. (lbs.)	Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	F	W	Chorea	68	M	91	10	9.5	12	12	13.5	15	22.5	18	15	10	18	26	22.5	28	23.5	25	25	22.5	16	13			
2	G	R	Chorea	65	M	62	10	10	9.5	12.5	14.5	17	19	20	18	19	20.5	27.5	23	10	18	17	18	15	18	16	11	12.5	10.5
3	H	A	R	68	F	108	10	10	9	11.5	15	21	22.5	12	23.5	26	27	34	27	35	50	50	26	26	27	15	11	12.5	12.5
4	A	W	Acute	70	M	86	11	14.5	12	16	22.5	20.5	23	30	24	25	27	30	37	44	26	29	13	11.5	10.5				
5	F	M	Reflex	41	M	57	10	11	16	21.5	25	24	36	25	27	21.5	10	12	31	39	35	19	15	9.5	16				
6	W		Chorea	10	M	23	10	12	11.5	13.5	16	16	17	15.5	14	13	10	10	9.5		18	15							
7	H	A	Chorea	72	M	81	11	9	10.5	15	17.5	24	21	29	26	18	12	11	12		15	14	12	10					

nitrogen and glucose determination, the cephalin-cholesterol flocculation test, and hippuric acid liver function test, were all within normal limits. She was given 540 mg. (5 mg. kilo) of this dicoumarin on the day that dilatation, biopsy, and cauterization of the cervix and curettage of the uterus was performed under cyclopropane and nitrous oxide anesthesia. Thereafter the patient received daily doses of 162 mg. (1.5 mg. kilo). On the fifth day following operation, 7 days prior to the regular menstrual period, she began to have vaginal bleeding. Bleeding was not excessive until the eighth postoperative day, when the drug was discontinued. On this day the coagulation time was 23 minutes, the prothrombin time 19.5 seconds. Profuse to moderate bleeding persisted for 9 more days. Five transfusions of fresh whole blood, 500 cc. each, were given between the ninth and eighteenth postoperative days, spaced as shown in the table. Despite the transfusions the hemoglobin fell from a level of 15.9 gm. on the day of operation to 11.1 gm. the day following the last transfusion. No gross bleeding was demonstrated from any other than the site of the operation.

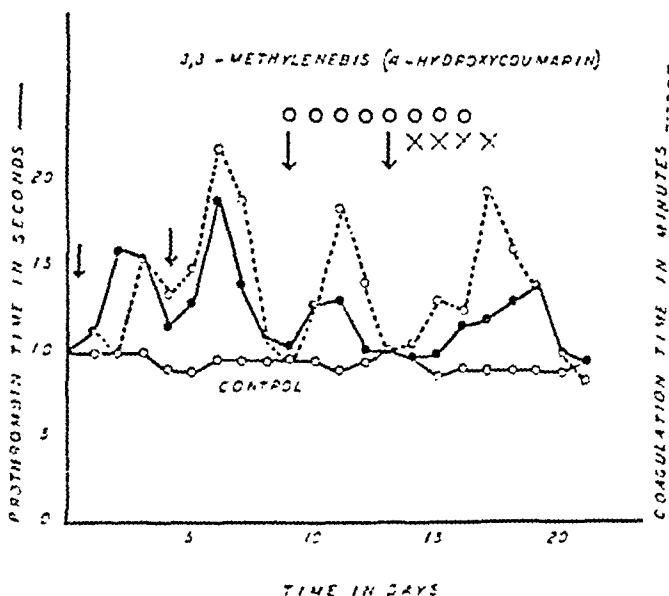


CHART 1. Effect of repeated oral doses of dicoumarin on the prothrombin time and coagulation time of a 71-kg. white male. \downarrow indicates a 5-mg. dose and \times a 1-mg. dose. \circ indicates a 10-mg. oral dose of 2-methyl-1,4-naphthoquinone. The reversible effect of the vitamin K administration is shown.

This patient gave us much concern during the period of bleeding. The first 4 transfusions were temporarily beneficial but not completely corrective. It is possible that larger quantities of blood might have been more effective. By the eighteenth postoperative day the patient had not received the dicoumarin for 9 days. It may be said that the administration of the substance to a patient that has had curettement of a mucous membrane surface is unusual and the risk of hemorrhage is great.

This case emphasizes one of the inherent limitations in the use of this dicoumarin, namely, the protracted decrease in coagulability of

the blood. The effect may be great and prolonged for days after the medication has been stopped, thus suggesting a cumulative effect of the drug. A similar effect had been previously observed in dogs.

Effect of Vitamin K. It has been shown that the simultaneous administration of vitamin K orally or intramuscularly to dogs in 1-mg. and 2-mg. doses did not inhibit the prothrombin-lengthening effect of the dicoumarin. Recent studies demonstrate that doses as large as 10 mg. of 2-methyl-1, 4-naphthoquinone to human beings do not prevent the lengthening of the prothrombin time and coagulation time. Chart 4 demonstrates the lack of gross effect of synthetic vitamin K upon the prothrombin and coagulation time.

Effect of Transfusions. Although the administration of vitamin K is not an antidote for the effects of the dicoumarin, it has been our experience that a transfusion of blood will shorten the prothrombin time and coagulation time. A quantity greater than 500 cc. may occasionally be necessary for satisfactory results. This effect is often transient, usually of about 24 hours' duration, and repetition of the transfusion may be necessary. This corrective effect confirms the finding of Schofield^{8a,b} and Roderick⁷ that the lives of cattle with serious hemorrhage can be saved by transfusions of serum or whole blood.

The effect of transfusions has been demonstrated 13 times in 8 patients. Fresh blood was found to be preferable, but bank blood, if not too old, appeared to be partially effective. The effect in the one case where fresh citrated blood was used is shown in Case 3 (Table 1), details of which are given above. This was the only case where transfusions were given to control bleeding. After 4 of the 5 transfusions the bleeding was less but not completely controlled. In other patients with less marked prolongation of prothrombin and coagulation time, transfusions were effective in bringing about a temporary return to normal levels.

Discussion. The use of 3,3'-methylenebis (4-hydroxycoumarin) to prolong coagulation of the blood in human beings appears feasible. Its administration, orally or intravenously, cautiously carried out, has not been attended by any symptoms of toxicity other than hemorrhage. Blood in microscopic quantities, as demonstrated by positive benzidine tests, appeared in the urine of 10 of the 73 patients at the height of the response. In 4 patients occult blood by the guaiac test was found in the stool. The case cited above, where curettement of the uterus was performed at the time the dicoumarin was being administered was the only one where gross bleeding occurred. The bleeding was restricted to the operative site.

The advantages of the dicoumarin as a possible substitute for heparin in the prevention of thromboses are quite obvious. The dicoumarin may be produced relatively cheaply, it may be given by mouth or intravenously, and a prolonged effect is obtainable. The

therapeutic index appears to be high. Doses as great as 25 mg. per kilo may be given intravenously to dogs without producing serious effect, whereas doses of 3 to 5 mg. per kilo will produce the desired prolongation of coagulation. The inevitable latent period after administration is a disadvantage in certain cases where immediate prolongation of the coagulation time is desired. There is, however, no theoretical objection to immediate treatment with heparin and subsequent substitution of the dicoumarin. The probable additional disadvantages are the apparent greater toxicity of this dicoumarin in excessive doses and the fact that once the coagulation is prolonged it cannot be shortened quickly by withholding the drug. We have given this drug in suitable doses orally each day for as long as 5 weeks without discernible toxic effect.

Whether or not 3,3'-methylenebis (4-hydroxycoumarin) or one of its derivatives will be efficacious, as heparin appears to be, in preventing thrombosis, is still to be determined. Our main purpose to date has been to establish a reasonably safe dosage. We have given it to only 6 patients with thromboses and to none for the distinct purpose of preventing thrombosis. Much study will be necessary to settle this major point of therapeutic efficacy.

This dicoumarin is potentially capable of inducing undesirable hemorrhage even in a dosage which is considered to be within the therapeutic range. It is our firm belief that its indiscriminate use would be extremely hazardous, and we urge that those who employ it administer the minimal effective dose and avoid its use where gross hepatic disease is known to exist. Because of considerable individual variation in response, it is imperative for the present that the prothrombin time and coagulation time be measured not less often than once a day. The desired degree of prolongation of coagulation is not known with certainty, but it appears that a coagulation time of approximately 15 to 20 minutes should be suitable and not too hazardous. Prolongation in the prothrombin time to between 12.5 and 19 seconds (approximately 50% to 25% of normal) is probably reasonably safe. At the 19-second level the percentage of prothrombin in the blood by the method we use is approximately 25%, and lower levels are not desirable.

At the present time it is our opinion that simultaneous determinations of the prothrombin time cannot be omitted. Although the lessening of coagulability of the blood is crucial, a check upon the cruder technical procedure of determining the coagulation time of whole blood is desirable. The determination of the prothrombin time is less subject to error in the hands of trained workers.

The administration of 3,3'-methylenebis (4-hydroxycoumarin) produced prolongation of the prothrombin time and coagulation time. Whether or not the coagulation time is prolonged because of the decrease in prothrombin is not established beyond question although there is, in most instances, a parallelism. The manner in which the dicoumarin acts to produce prolongation in the pro-

thrombin time after the latent period is not known. The theory that seems most attractive is that it acts as a physiologic inhibitor of prothrombin formation by the liver and that during the latent period the prothrombin of the blood is depleted. This possibility of liver inhibition is strengthened by the fact that vitamin K administration in adequate dosage is ineffective in preventing the increase in prothrombin time.

A second possibility is that the prothrombin produced in the presence of the hemorrhagic agent is altered in such a way that it is inactivated. The latent period might be due to some change that the dicoumarin must undergo in the body during the latent period before it is capable of functioning. Studies in progress by W. R. Sullivan, R. S. Overman, M. A. Stahman, and K. P. Link indicate that the hemorrhagic action takes place after the molecule of the compound has undergone certain changes in the body.

Conclusions. 1. The administration of 3,3'-methylenebis (4-hydroxycoumarin)—here referred to as dicoumarin—to human beings produced prolongation in the prothrombin time and coagulation time. The dosage and mode of administration have been discussed.

2. The minimal effective dose should be employed. The necessary dose for the desired decrease in coagulability of the blood varies with the individual case; but it appears that an initial oral dose of 5 mg. per kilo with subsequent daily oral doses of 1.5 mg. per kilo is effective in most patients. A single intravenous dose of 4 mg. per kilo was found to be suitable and effective. This dose may be repeated when necessary.

3. During the period of observation the prothrombin time and coagulation time should be determined not less often than once daily. If the increase of prothrombin time or coagulation time becomes too great, the dicoumarin should be withheld temporarily, and, if necessary, blood transfusions of 300 to 600 cc. should be given.

4. One patient who received dicoumarin following curettage of the uterus developed gross hemorrhage locally. No other gross toxic effects attended the use of the material in 73 patients.

5. The administration of vitamin K did not prohibit or correct the prothrombin deficiency produced by 3,3'-methylenebis (4-hydroxycoumarin).

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THE RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND DEGREE OF TUBULAR REABSORPTION OF GLUCOSE IN RENAL GLYCOSURIA.*

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ALTHOUGH various studies have indicated that true renal glycosuria is not associated with renal disease^{1,5,9} or derangement in glomerular function,¹⁶ no comprehensive and quantitative study has been made of the renal blood flow and the degree of renal tubular reabsorption of glucose at increasing plasma concentrations of glucose in this condition.

This communication presents simultaneous measurements of the glomerular filtration rate, the renal blood flow, the filtration fraction and the tubular reabsorption of glucose at different plasma concentrations of glucose in 5 patients with moderate renal glycosuria and in 7 controls.

Methods. The diodrast and inulin clearance methods were utilized for the estimation of the effective renal blood flow and the rate of glomerular filtration respectively. The same procedure for these two determinations was followed as previously described⁷ except that the priming infusion in the present investigation consisted of (a) 50 cc. of 10% inulin solution, (b) 50 cc. of 50% glucose and (c) 1 cc. of 35% diodrast solution. The sustaining infusion consisted of (a) 100 cc. of 10% inulin solution, (b) 400 cc. of 50% glucose solution, (c) 5 cc. of 35% diodrast solution and (d) 250 cc. of normal saline. All clearances were adjusted to 1.73 sq. m. of surface area.

Blood samples were taken 30, 60, 90 and 120 minutes after the sustaining infusion had been started. Total urine collections were taken 45, 60, 75, 90, 105 and 120 minutes after the sustaining infusion had been started. For the first 30 minutes, the sustaining infusion was allowed to enter at a rate of 3 cc. per minute. This rate was increased 2 cc. every 30 minutes so that, at the end of the experiment, the patient was receiving 10 cc. of sustaining infusion per minute. At the end of 60 minutes, the patient was also given an additional 50 cc. of 50% glucose solution. In this manner, the three

* This work was aided by a grant from the Department of Medical Research of the Western Post Office at Chicago.

essential measurements were determined at constantly increasing blood glucose concentrations.

The blood and urine collections were analyzed for glucose, according to the method of Folin,⁶ diodrast iodine, according to the method of White and Rolf¹⁷ and inulin, according to the method of Alving and associates.²

The determination of tubular reabsorption of glucose was performed according to the principles given by Shannon and Fisher¹⁵ and Goldring, Chasis, Ranges and Smith.⁸ The glucose filtered through the glomeruli was calculated as the product of the inulin clearance X the plasma concentration of glucose. The tubular reabsorption of glucose was calculated as the difference between the amount of glucose filtered through the glomeruli (mg. per minute) and the amount of glucose found in the urine (mg. per minute).

The renal glucose reabsorption index (R.G.I.) was calculated as the ratio: $\frac{\text{glucose filtered through glomeruli (mg. per minute)}}{\text{glucose reabsorbed by tubules (mg. per minute)}}$. This index was used because it allowed a comparative evaluation of the degree of tubular reabsorption of glucose in any particular case, regardless of the rate of glomerular filtration. Diminished reabsorption, then, would be expressed by a high index, increased reabsorption, by a low index.

The 7 normal individuals studied had normal blood pressure and had no signs or symptoms of kidney disease. The urine of each was negative for detectable glucose by the Benedict test before and two hours after the ingestion of 100 gm. of glucose. The fasting plasma sugar of each was also within normal limits.

The pertinent data concerning the patients with renal glycosuria are given below. Each of the 5 patients had a glycosuria without hyperglycemia; the sugar in the urine was found to be glucose; and all urine specimens were found to contain detectable glucose. In 4 of the 5 cases, there was no progression in the glycosuria, despite the fact that they had been observed over several years. The fifth case was discovered 3 weeks prior to our examination. These cases then conform in general to the essential criteria postulated by Marble.¹²

CASE 1. E. N., male, aged 41, was known to have had renal glycosuria for at least 6 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 86.2 mg. per 100 cc. and the fasting urine concentration of sugar was 118.3 mg. per 100 cc. The plasma concentration of glucose, 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 134.2, 146.0 and 91.7 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 202.0, 449.4 and 206.2 mg. per 100 cc. respectively. The chemical and microscopic examination of the urine was within normal limits.

CASE 2. L. L., male, aged 49, was known to have had renal glycosuria for at least 3 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 81.6 mg. per 100 cc. and the fasting urine concentration of sugar was 158.8 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 77.0, 123.5 and 133.0 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 138.0, 300.8 and 330.6 mg. per 100 cc. respectively. The chemical and microscopic examination of the urine was otherwise negative. The blood pressure was within normal limits.

CASE 3. N. P., male, aged 30, was known to have had renal glycosuria for at least 5 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 83.7 mg. per 100 cc. and the fasting urine concentration of sugar was 238 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 69.7, 106.4 and 97.1 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 336, 320 and 340 mg. per 100 cc. The chemical and microscopic examination of the urine was otherwise negative. The blood pressure was within normal limits.

CASE 4. J. C., male, aged 40, was known to have had renal glycosuria for at least 3 weeks prior to the present examination. He was first seen in the Department of Medicine, University of California Medical School, and was referred to us for further study. He had no symptoms. The fasting plasma concentration of glucose was 74.6 mg. per 100 cc. and the fasting urine concentration of sugar was 155.0 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 155.6, 158.8 and 63.9 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 347.8, 384.6 and 357.2 mg. per 100 cc. respectively. The chemical and microscopic examination of urine was otherwise negative. The blood pressure was within normal limits.

CASE 5. F. Y., male, aged 35, was known to have had renal glycosuria for at least 5 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 90.9 mg. per 100 cc. and the fasting urine concentration of sugar was 46.5 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 141.8, 141.4 and 142.6 mg. per 100 cc. respectively. The last plasma sugar remained elevated because an 18% glucose solution was given intravenously 110 minutes after the beginning of the glucose tolerance test. The sugar concentrations of the urine collections taken at the same time intervals were 183.4, 540.4 and 695 mg. per 100 cc. respectively. The blood pressure was within normal limits.

TABLE I.—CLEARANCE DETERMINATIONS IN NORMAL AND RENAL GLYCOSURIC INDIVIDUALS.

A. Normal.

Case No.	Name	Age	Effective renal blood flow (cc. per min.)	Renal insulin clearance (cc. per min.)	Filtration fraction %
1	H. R.	43	1400	108	12.8
2	E. B.	16	1370	109	12.4
3	K. D.	32	—	145	—
4	O. F.	23	1640	234	20.3
5	E. K.	32	—	116	—
6	R. R.	23	1035	110	19.0
7	S. S.	50	865	112	21.7
Average			1262	133	17.2

B. Renal Glycosuria

1	E. N.	41	1500	159	19.6
2	L. L.	49	1470	118	13.9
3	N. P.	30	1010	127	20.4
4	J. C.	40	1135	127	14.8
5	F. Y.	35	930	103	20.9
Average			1279	127	17.9

Results A. *The Renal Blood Flow and Glomerular Filtration in the Normal and Glycosuric Individual.* No abnormal change in the

effective renal blood flow, the rate of glomerular filtration or the filtration fraction was found in the 5 renal glycosuric patients studied. The average effective renal blood flow was 1262 cc. per minute in the 7 control patients (see Table 1) and 1269 cc. per minute in the glycosuric patients. The average inulin clearance was 133 cc. per minute in the control and 127 cc. per minute in the glycosuric group. The close similarity of these values with those previously reported by us^{7b} indicates also that the production of a hyperglycemia and its accompanying profuse diuresis does not change the renal blood flow or glomerular filtration.

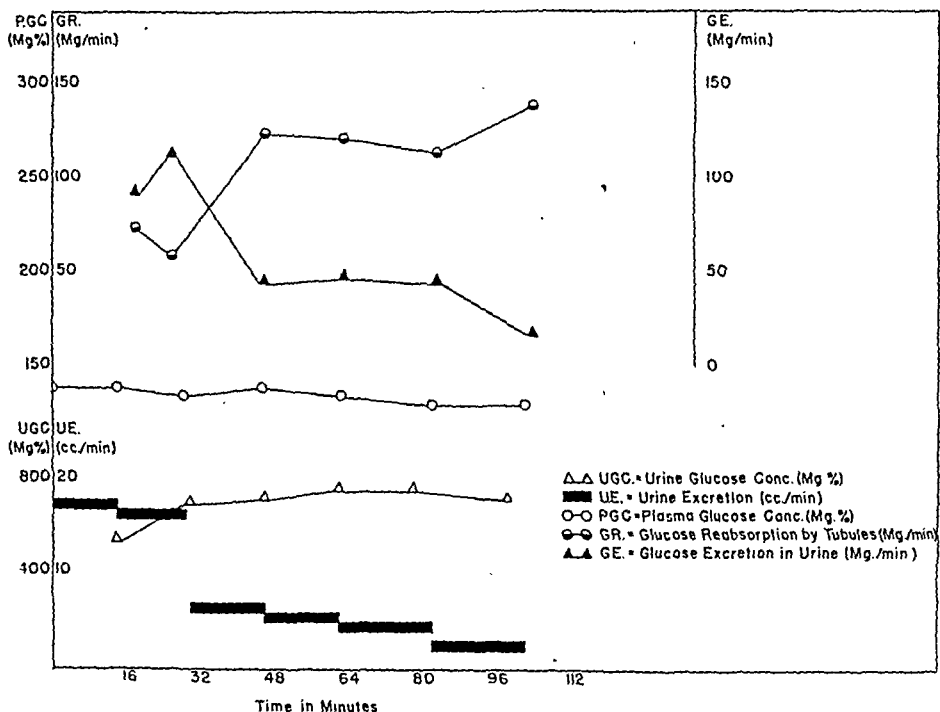


CHART 1.—Relation of tubular reabsorption of glucose to excretion of urine at constant plasma concentrations of glucose. The dependence of urinary glucose concentration upon the plasma concentration of glucose also is shown (Case F. Y.).

B. The Tubular Reabsorption of Glucose in the Normal and Glycosuric Individual. In both the normal and the glycosuric individual, it was found that the urinary concentration of glucose at high plasma glucose levels (100 to 400 mg. per 100 cc.) was relatively independent of the rate of urine excretion but was directly proportional to the concentration of glucose in the plasma. This independence of the urine concentration of glucose and the rate of urine excretion is illustrated in Chart 1. Here, the plasma glucose is maintained at a constant level and the rate of urine excretion decreases. Nevertheless, there is little change in the urinary concentration of glucose. The degree of tubular reabsorption, therefore, at a constant plasma concentration of glucose (Chart 1), increases with

TABLE 2.—THE GLOMERULAR CLEARANCE AND TUBULAR REABSORPTION OF GLUCOSE IN NORMAL AND IN RENAL GLYCOSURIC INDIVIDUALS AT INCREASING BLOOD GLUCOSE LEVELS.

Normal.

Plasma Glucose, 100 to 200 Mg. per 100 Cc.

Case No.	Name.	Plasma glucose concentration (mg. per 100 cc.).	Urine flow (cc. per min.).	Glomerular clearance of glucose (mg. per min.).	Tubular reabsorption of glucose (mg. per min.).	Renal glucose reabsorption index.
1	H. R.	116	6 60	123	120 0	1 03
2	E. B.	140	4 20	159	155 0	1 03
3	K. D.					
4	O. F.	115	6 66	273	268 0	1 02
5	F. K.					
6	R. R.	162	2 05	160	159 0	1 02
7	S. S.	129	1 50	145	141 0	1 03
Average		132	4 20	172	169 0	1 03

Plasma Glucose, 200 to 300 Mg. per 100 Cc.

1	H. R.	298	3 58	316	300 0	1 05
2	E. B.	275	5 60	312	292 0	1 07
3	K. D.	263	3 45	373	358 0	1 04
4	O. F.	241	8 20	575	504 0	1 14
5	F. K.	254	7 50	264	207 1	1 28
6	R. R.	292	3 60	289	261 0	1 11
7	S. S.	247	4 70	278	246 0	1 13
Average		267	5 23	344	309 0	1 12

Plasma Glucose, 300 to 400 Mg. per 100 Cc.

1	H. R.	356	7 36	377	350 0	1 08
2	E. B.	385	12 35	438	385 0	1 14
3	K. D.	338	10 50	476	436 0	1 10
4	O. F.	305	16 10	727	618 0	1 18
5	F. K.	380	11 75	395	298 0	1 32
6	R. R.					
7	S. S.	341	4 70	384	349 0	1 10
Average		351	10 46	466	406 0	1 15

Renal Glycosuria.

Plasma Glucose, 100 to 200 Mg. per 100 Cc.

1	E. N.	110	3 84	186	168 3	1 11
2	L. L.	128	10 80	175	139 0	1 26
3	N. P.	102	2 30	140	131 0	1 07
4	J. C.	111	4 01	141	126 6	1 12
5	F. Y.	133	3 15	160	137 3	1 17
Average		123	4 83	160	140 4	1 15

Plasma Glucose, 200 to 300 Mg. per 100 Cc.

1	E. N.	270	5 00	431	399 8	1 08
2	L. L.					
3	N. P.	284	4 68	453	419 0	1 08
4	J. C.					
5	F. Y.					
Average		272	4 84	462	409 4	1 08

Plasma Glucose, 300 to 400 Mg. per 100 Cc.

1	E. N.	400	10 50	508	475 0	1 07
2	L. L.	350	11 00	425	419 0	1 02
3	N. P.	300	12 16	546	422 0	1 17
4	J. C.	241	2 16	467	394 0	1 04
5	F. Y.					
Average		347	9 77	479	447 0	1 05

decreasing urine flow. In any study then, of the renal tubular reabsorption of glucose in several groups of individuals, a comparison of the results may not be valid unless the plasma concentrations of glucose and the rates of urine excretion of both groups are approximately equal.

As Table 2 indicates, the kidney of the glycosuric individual at a moderate plasma level of glucose (100 to 200 mg. per 100 cc.) is less efficient than that of the normal individual in reabsorbing glucose contained in the glomerular filtrate. Whereas, in both types of individuals, the average plasma concentration of glucose, the glomerular clearance of glucose and rate of urine excretion were approximately equal, the average rate of tubular reabsorption of glucose was distinctly less in the renal glycosuric (140.4 mg. per minute). The average R.G.I., therefore, was higher in the glycosuric group (1.15) than in the control group (1.03).

When the two groups were studied at higher plasma levels of glucose (200 to 300 mg. per 100 cc.) it was found (see Table 2) that, although the tubular reabsorption of glucose (309 mg. per minute) increased in the normal group, the glomerular clearance of glucose (344 mg. per minute) increased relatively more. The average R.G.I. (1.12) therefore was increased. Unfortunately, only 2 glycosuric individuals were studied at this particular plasma glucose range, but, unlike the normal individuals, these 2 did not show an increased divergency between the glomerular clearance of glucose (442 mg. per minute) and the tubular reabsorption of glucose (409.4 mg. per minute). The average R.G.I. (1.08) accordingly was not increased.

Finally, the tubular reabsorption of glucose in these two groups was studied at a very high plasma level of glucose (300 to 400 mg. per 100 cc.). In the control group, the glomerular clearance of glucose (466 mg. per minute) was found again to have increased relatively more than the tubular reabsorption of glucose (406 mg. per minute). The average R.G.I. (1.15), accordingly, was increased. In contrast to these findings, there was no increasing divergency between the glomerular clearance of glucose (470 mg. per minute) and the tubular reabsorption of glucose (437 mg. per minute) in the glycosuric group. On the contrary, in the glycosuric individuals there was less inequality between these two renal functions at this plasma glucose range than at the lowest range studied. This last fact resulted in a lower average R.G.I. (1.08) for the glycosuric individuals at the maximum plasma glucose range studied. These results indicated that the efficiency of tubular reabsorption of glucose increased with rising plasma concentrations of glucose in the glycosuric individual and decreased in the control subjects.

Discussion. The studies herein reported indicate clearly that the effective renal blood flow, the glomerular filtration and the filtration fraction are within normal limits in the individual with moderate

renal glycosuria. Furthermore, the present observations indicate that, whereas tubular reabsorption of glucose in the glycosuric patient is less than that found in the non-glycosuric individual at moderate plasma concentrations of glucose (100 to 200 mg. per 100 cc.), this comparative diminution in reabsorption in the glycosuric subject disappears at higher plasma concentrations of glucose. As a matter of fact, it would appear as if the renal glycosuric individual absorbs glucose contained in the tubular fluid more efficiently than does the non-glycosuric individual at high plasma concentrations of glucose. This last observation makes it difficult to assume that a serious organic or physiologic derangement is present, either in the kidney or elsewhere, in the patient with moderate renal glycosuria; for one would not expect a fundamentally deranged organ to perform abnormally when not under stress and normally when under considerable stress.

Several investigators,^{11,14} however, have attempted to incriminate the adrenal or parathyroid gland in this disorder. Their evidence, is not conclusive. Furthermore, other studies^{3,4} have denied the relationship of any particular endocrine gland with the etiology of renal glycosuria.

Indeed, it is perhaps questionable whether the individual with moderate renal glycosuria should be considered abnormal in the pathologic sense, for there is uniform agreement^{5,9,10} that a considerable portion of supposedly normal people will have glycosuria without hyperglycemia during the administration of a glucose tolerance test. Thus, the mild glycosuric individual may be the statistical victim of too close adherence to an average renal threshold value composed of widely scattered individual values. Certainly our results are compatible with this latter view.

Conclusions. 1. The effective renal blood flow (diodrast clearance) and the rate of glomerular filtration and the degree of renal tubular reabsorption of glucose were studied in 7 normal and 5 renal glycosuric individuals.

2. The effective renal blood flow and glomerular filtration in the renal glycosuric individual were found to be normal.

3. The lessened tubular reabsorption of glucose in the renal glycosuric individual does not appear to be due to an organic kidney defect, for at plasma glucose levels above 200 mg. per 100 cc., the efficiency of tubular reabsorption of glucose in these cases equals or exceeds that found in non-glycosuric individuals.

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IMMUNITY IN DIABETES.

IV. MEASUREMENTS OF PHAGOCYTTIC ACTIVITY IN DIABETES MELLITUS.

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THIS study is part of an investigation of the well-known susceptibility of diabetic patients to infection. It is evident from clinical observation that this susceptibility varies with changes in the condition of the patient. In a previous paper^{1c} it was suggested that, in such a study, all of the offensive and defensive properties, both of the infecting organism and of the tissues and fluids of the host, should be examined were this possible. It seems probable that at least some of these properties would differ in the diabetic as compared with the non-diabetic and also with the state of adjustment of the patient. In former papers of this series^{4b} it has been shown that some of the constituent substances in the blood of diabetic patients and experimental animals show no significant alterations which would connect them with this deficiency in resistance. On the other hand, there does appear to be a significant correlation between some of these factors, such as the amount of glycogen in the tissues and of globulin in the blood, and the ability of the body to resist infection or at least to delay its effects. As regards the globulin, these observations would seem to be not altogether unexpected, as much previous work has shown that there exists a close connection between globulin and various phases of immunity.

The present study deals with the ability of the leukocytes of the host to phagocytize such bacteria as may be present in the body. The phagocytes are known to be affected by a number of conditions, some of which, it seems, might be altered in the diabetic patient depending on the state of adjustment. It has been shown that a decrease in the phagocytic ability of these cells occurs with lowered

temperature,² increased hydrogen-ion concentration and in the presence of certain substances, including iodine and lactic acid. Increase of cytoplasmic viscosity also has been reported as decreasing phagocytic action. On the other hand, addition *in vitro* of histamine, calcium ions and certain fat-soluble substances including iodoform, chloral hydrate, ethyl alcohol and low concentrations of chloroform, appear to increase phagocytosis. Turnya found a lowered phagocytosis in thyroidectomized rabbits. This was increased by feeding thyroid extract.²

Methods. In this study the phagocytic power of the leukocytes has been measured by a method devised by Boerner and Mudd.¹ This method consists in adding to 1 cc. of freshly drawn blood to which a small amount of heparin has been added, 0.1 cc. of a suspension of bacteria in physiologic saline, prepared so that the suspension always contains approximately the same number of bacteria. The dilution in these determinations was such that in each 0.1 cc. of suspension there were 200 million bacteria. As the fortuitous collision of cells and bacteria is an important factor in phagocytosis, a variation in the number of bacteria used will alter the number engulfed by the cells. The blood, with added bacteria, is agitated at 38° C. in the type of water bath devised by Boerner and Mudd.¹ At intervals of 3, 6, 9 and 12 minutes, a drop of blood is removed and smears are made on glass slides according to standard technique. After rapid drying, these smears are stained by Giemsa's stain and the number of bacteria in 100 leukocytes is counted. The "phagocytic score," which is the term used by Mudd and his associates to denote the phagocytic ability of the cells, as demonstrated by this method, expresses the number of bacteria taken up by 100 cells as a percentage of a theoretical maximum of 30 bacteria per cell. In these determinations, smears were made after 6 minutes and 12 minutes agitation. The results given in this paper were from slides made after 12 minutes. The *Staph. aureus* used in this investigation was obtained from the blood of a fatal case of bacteremia and has been maintained for the past 6 years by semi-weekly transplants on plain agar. Only smooth colonies are taken for transplant so that at the present time very few rough colonies appear in the culture. This same strain of *Staph. aureus* has been used throughout all of the experiments reported in this series of papers.

The sugar of the blood was determined by the modification of Folin's micro method, the final reading being made with an Evelyn photoelectric colorimeter. Bloor's method was used for determination of cholesterol and the Pregl-Kjeldahl method for total protein and for albumin after fractionation by a 22.2% solution of sodium sulphate at 37.5° C. Globulin was taken as the difference between the total protein and the albumin. The diabetic patients on whom these studies were made were taken from the Metabolic Clinic of this hospital and are typical of such patients in a fair state of metabolic adjustment. The normal controls were doctors, students

from +22 to -16 with an average change, regardless of sign, of 5.23. The phagocytic score of all 54 diabetic patients ranged from 13 to 53 (average 28); S. D. 1.12.

In Table 1 are shown the distribution of phagocytic scores in diabetic patients and normal controls. No significant difference can be recognized.

TABLE 1.—DISTRIBUTION OF PHAGOCYTIC SCORES IN NORMAL CONTROLS AND DIABETIC PATIENTS.

Phagocytic scores.	Normal controls (17).	Diabetic patients (78).
Above 40	29%	23%
20 to 40	53%	55%
Below 20	18%	22%

Number of observations is shown in parentheses.

At the same time that blood was taken for determination of the phagocytic score, blood was also removed for determination of the sugar and of the cholesterol, total protein and albumin of the serum. As has been stated, the serum globulin was measured as the difference between the total protein and the albumin. The results of these examinations are shown in Table 2.

TABLE 2.—CHEMICAL ANALYSES OF BLOOD AND PHAGOCYTIC SCORES IN PATIENTS WITH DIABETES.

	Patients not taking insulin.	Phagocytic score.	Patients taking insulin.	Phagocytic score.
Blood sugar	<i>Up to 139 mg. (28)</i> 140 mg. and above (20)	26 27	<i>Up to 139 mg. (32)</i> 140 to 250 mg. (35) 250 mg. and above (14)	27 28 27
Serum cholesterol	<i>Up to 255 mg. (8)</i> 256 to 349 mg. (22) 350 mg. and above (7)	27 28 28	<i>Up to 255 mg. (26)</i> 256 to 350 mg. (44) 350 mg. and above (12)	25 29 25
Serum protein	6.20% to 8.49% (26) 8.50% and above (14)	29 25	6.2% to 8.5% (54) 8.5% and above (25)	27 28
Serum albumin	<i>Up to 4.2% (12)</i> 4.3% to 5.7% (36)	28 26	<i>Up to 3.8% (10)</i> 3.9% to 4.2% (28) 4.3% to 5.7% (36)	24 28 29
Serum globulin	1.3% to 3.3% (13) 3.4% and above (24)	31 29	1.3% to 3.3% (24) 3.4% and above (58)	25 29

Number of observations in each group is shown in parentheses.

It appears from these figures that the variations in the chemistry of the blood commonly found in diabetes show no correlation with the phagocytic power of the blood. Phagocytic score varies little when the components measured in the chemical tests are exhibiting considerable variation. It will also be noted that the percentages of patients showing high, medium and low scores is similar to those found in the normal controls. On the whole, it would seem that diabetes in the absence of any marked complications does not alter the phagocytic power of the leukocytes as tested by this method.

Since it appears that reasonably well-balanced diabetic patients do not commonly differ from normal controls, in this test of the ability of the phagocytes to engulf bacteria, it seemed desirable to test the influence of various factors upon the diabetic patient's

phagocytic scores. For this purpose two common complications, acidosis and undernutrition, were selected and also the response of the diabetic to the stimulus of antityphoid vaccination. Six patients with acidosis were studied in this way. The results are shown in Table 3. Accompanying the leukocytosis, which is a common finding in this condition, there is a very definite decrease in the phagocytic score. The highest figure among the acidosis patients was only slightly higher than the lowest in those diabetics without acidosis. The average of the six examinations is 9 ± 1.4 as compared with 28 ± 2.0 in those patients shown in Table 2. The sugars of the blood varied as would be expected from 220 to 512 with four of them over 400. The total protein, albumin, and globulin, of the serum varied considerably, probably following the marked dehydration and other alterations of the blood and tissues in these patients. The serum cholesterol was not found to be as high as might have been expected, perhaps due to the short time during which the acidosis had developed.

TABLE 3.—PHAGOCYTIC SCORE OF DIABETIC PATIENTS WITH ACIDOSIS.

Patient.	Date.	Blood sugar, mg. per 100 cc.	CO ₂ content, vols. %.	Serum cholesterol, mg. per 100 cc.	Serum protein, %.	Serum albumin, %.	Globulin, %.	Phagocytic score.	Age, yrs.
J. B.	12 9 38	488	16	287	9.94	4.50	5.44	8	37
D. Mc.	1 23 39	380	18	<i>q.n.s.</i>	6.90	5.39	1.51	10	19
R. M.	1/ 6 39	220	28	416	11.30	4.00	7.30	6	17
R. W.	1 16 39	512	30	219	7.87	3.98	3.89	8	16
M. L.	1 12 39	500	39	214	7.36	2.82	4.54	14	35
R. D.	3 18 39	486	19	316	8.32	4.09	4.53	8	29

Average phagocytic score, 9 ± 1.4 .

In Table 4 are shown the phagocytic scores and the results of the blood chemistry determinations in 6 diabetic patients who came into the hospital after inadequate treatment. They were all in a marked state of undernutrition with the usual signs of an uncontrolled diabetes. While these patients did not show quite as low a phagocytic power as those in acidosis, nevertheless it was significantly lower than was found in those diabetic patients who were in a fair state of control. It will be noticed that the CO₂ content of the serum, while close to the lower limit of normal, is definitely above the figures found in the patients with acidosis. The phagocytic scores, while slightly above those present in acidosis, are still significantly lower than those found in diabetic patients without complications.

In the course of an investigation of the ability of diabetic patients and normal controls to form agglutinins after inoculation with *B. typhosus* vaccine, the phagocytic score was determined, using the *Staph. aureus* suspension, and the agglutinins in the serum were determined by Dreyer's macroscopic method using a formalized suspension of *B. typhosus*. The vaccine was given according to the standard method. Blood for determination of the phagocytic power against *Staph. aureus* and of agglutinins against *B. typhosus* was taken before the first injection of the vaccine and 2 weeks after the third dose. Twelve diabetic patients and 8 normal controls were used. The patients varied in their state of adjustment. Five of them were in good condition, with hyperglycemia occurring only rarely, while the other 7 were less well balanced, yet in a fair state of adjustment, so that while hyperglycemia was not infrequent, there were no symptoms referable to the diabetes. The normal controls were members of a class of nurses entering the hospital at that time.

TABLE 4.—PHAGOCYTIC SCORE OF PATIENTS WITH UNCONTROLLED DIABETES.

Patient.	Date.	Blood sugar, mg. per 100 cc.	CO ₂ content, vols. %.	Serum cholesterol, mg. per 100 cc.	Serum protein, %.	Serum albumin, %.	Globulin, %.	Phagocytic score.	Age, yrs.
W. H.	12/ 8/38	476	51	q.n.s.	10.50	3.90	6.60	10	24
M. B.	1/17/39	346	51	250	7.12	3.17	3.95	19	40
C. R.	2/ 2/39	488	52	312	7.65	4.73	2.92	11	18
R. K.	1/17/39	256	60	240	8.27	4.00	4.27	9	
G. W.	2/15/39	298	57	219	7.43	3.90	3.53	16	32
H. G.	3/28/39	384	53	354	8.62	4.09	4.53	12	26

Average phagocytic score, 13 \pm 1.6.

Phagocytic scores against *Staph. aureus* and agglutinative titer against *B. typhosus* of these patients are shown in Table 5. It will be noticed that there is a significantly higher average in the phagocytic score in the normal controls after the vaccine as compared with the determinations made before the vaccine was given. On the other hand, no such difference is found in the patients before and after the vaccine; in fact, the average for these examinations are identical.

Inspection of Table 5 shows that after vaccination the controls exceed the diabetic patients both in phagocytic score and in agglutinative titer.

It has been generally believed that phagocytosis is influenced both by non-specific and by specific factors. These experiments show

that a non-specific increase in the activity of the phagocytes may occur following the injection of a bacterial antigen in the normal subject but that this increase failed to occur in the diabetics.

TABLE 5.—PHAGOCYTIC SCORE AND AGGLUTININATIVE TITER IN DIABETIC PATIENTS AND NORMAL CONTROLS BEFORE AND AFTER B. TYPHOSUS VACCINE.

	Before vaccine.		After vaccine.	
	Phagocytic score.	Agglutinative titer, dilution.	Phagocytic score.	Agglutinative titer, dilution.
Diabetic patients (12)	22	0	22	1 : 63
Normal controls (8)	21 ± 0.95	0	31 ± 1.50	1 : 540

Number of observations shown in parentheses.

During the progress of this work an investigation was being carried on with experimental animals. Depancreatized cats and normal controls were studied with respect to their ability to prevent the spread of bacteria to other parts of the body from a focus of infection in the skin. In addition to determinations of sugar of the blood and total protein, albumin and cholesterol of the serum, the phagocytic score against *Staph. aureus* was also determined. The results of these examinations confirm the observations reported above on diabetic patients. No alteration was found in the phagocytic score of depancreatized cats without complications as compared with that of normal control animals. On the other hand, those animals with a marked alteration in nutrition accompanying hyperglycemia showed a phagocytic score significantly lower than the control group. The animals with a large amount of acetone in the urine and a low CO₂ content of the serum also had a very low phagocytic score. No test of influence of typhoid vaccine on phagocytic score against *Staph. aureus* was made in these experimental animals but in an earlier study¹⁴ we found no difference in agglutination titer in typhoid vaccinated animals after depancreatization as compared with controls.

Discussion. It would appear from the above observations that the phagocytic power of the leukocytes is not affected by several alterations in blood chemistry that are commonly found in the diabetic patient who is in a fair state of control. This power may vary considerably but not more widely than is found in a group of normal controls. On the other hand, two complications of diabetes, namely, acidosis and the marked alteration in nutrition which often accompanies the extreme diabetic state, are associated with a significantly decreased ability on the part of the leukocytes to phagocytose.

Among the factors which are known to lessen phagocytosis are increased hydrogen-ion concentration of the body fluids. Increased viscosity of the fluids such as may be exhausted with dehydration, and the presence of organic acids diminish the activity of the phagocytes. Lactic acid especially is known to have an unfavorable influence on phagocytosis. These factors are all present to a greater

or less degree in the uncontrolled diabetic and may influence phagocytosis.

Furthermore, the stimulation of the phagocytic score against *Staph. aureus* by injection with typhoid vaccine occurs in the normal subject but not, in these experiments, in the diabetic patient. Taken with the inability of the diabetic organism to form agglutinins following *B. typhosus* vaccine, it would suggest that this restriction of response to stimulation may be an important factor in the failure of the diabetic organism to resist infection as well as controls.

Neufeld and Rimpau^{3a,b} suggested that the thermolabile opsonin of Wright is, like complement, general in its action and that the thermostable bacteriotropin, which they demonstrated in the serum after inoculation with pneumococci, is an antibody and specific in its action.

Support for Neufeld's theory is furnished by observations in this and former papers of this series. It has been shown^{4a} that complement in the serum of diabetic patients does not differ significantly in amount from that of normal controls; similarly the phagocytic score before vaccine does not differ in diabetic patients and normal controls. On the other hand, it has also been shown^{4a} that diabetics fail to form antibody in as high a titer after *B. typhosus* vaccine as do normal controls; similarly the diabetic patients are unable, after vaccine, to increase their phagocytic power as do normal controls. Before inoculation with vaccine we would be comparing opsonic activity in Neufeld's sense in the diabetic and control; after the use of vaccine the difference noted between diabetic and control would be referred to a difference in Neufeld's bacteriotropin.

Summary. 1. The phagocytic power of the leukocytes of diabetic patients and depancreatized cats and of normal controls has been determined (Boerner and Mudd¹).

2. Phagocytosis is found not to differ from normal in diabetic patients or in depancreatized cats in which the chemistry of the blood is within the limits commonly found in this condition.

3. Diabetic patients and depancreatized cats with acidosis or those with uncontrolled diabetes show a significantly decreased phagocytic power.

4. An increase of phagocytic activity of blood leukocytes which occurs in normal controls after typhoid vaccine, did not occur in our diabetic patients.

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STUDIES ON GALACTOSE TOLERANCE WITH ESPECIAL REFERENCE TO THYROID DISEASE.

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To clinicians faced with the problem of the diagnosis of hyperthyroidism, any new diagnostic test is most welcome, especially in distinguishing low-grade hyperthyroidism from anxiety states associated with hyperventilation or cardiac insufficiency. Such a procedure was recently proposed by Althausen *et al.*^{1,2,3,4} in the form of an oral galactose tolerance test. Their studies suggested that in hyperthyroidism the occurrence of glycosuria, impaired dextrose tolerance and postprandial hyperglycemia were due to increased rate of absorption of sugar from the intestinal tract. In accordance with Verzar's views,²⁵ this increased absorption is due to accelerated phosphorylation in the intestinal mucosa. Evidence was presented to show that other factors such as carbohydrate depletion, increased rate of bloodflow, intestinal hyperperistalsis, elevated basal metabolism and increased permeability of the mucosa did not play a part in the increased rate of intestinal absorption.²

Galactose was used in this test because its rate of absorption from the intestinal tract was found to be similar to that of glucose. It had the added advantage of being easily isolated from other blood-reducing substances. In addition, only the liver can utilize galactose^{8,9,11,17} and it is not influenced by insulin.¹² Furthermore, there is no renal threshold for galactose.¹⁴ The results^{1,3,4} indicated that the peak of the blood galactose in patients with hyperthyroidism after the oral administration of 40 gm. of galactose was three times that of normal subjects. The higher values were found at the 30 or 60 minutes' blood specimens and ranged between 10 to 30 mg. per 100 cc. for normal individuals. Values between 20 to 40 mg. per 100 cc. were considered in the doubtful range, while those over 40 mg. per 100 cc. were classified as definitely abnormal. In hypothyroid patients, the maximum rise in blood galactose did not exceed 10 mg. per 100 cc.

Althausen and his coworkers found that in patients with severe hyperthyroidism, the basal metabolic rate, however, was a better

indicator of the severity of thyrotoxicosis, although the galactose tolerance curves were also very high. Impaired galactose tolerance was also present in Paget's disease and in patients with jaundice due to parenchymatous liver involvement. Maclagan and Rundle¹⁶ likewise found postabsorptive curves which were elevated in hyperthyroid patients but they suggested that these curves were due to impaired liver function.

The present investigation was undertaken to restudy and to supplement the previous findings of Althausen and his coworkers. Moreover, it appeared important to determine the effect of age and of clinical conditions other than hyperthyroidism on galactose tolerance.

Material and Method. An oral galactose tolerance test as described below was carried out on each of 85 patients. The following groups were segregated:

1. *Age Group.* Forty-seven patients; 24 were over the age of 50 and 23 under 50 years in whom no evidence of thyroid disease, impaired liver function or Bright's disease was disclosed.

2. *Hyperthyroidism.* Twenty patients; 16 with diffuse toxic goiter and 4 with toxic nodular goiter.

3. *Impaired Liver Function.* Seven patients; 5 with toxic hepatitis due to sulfonamide or gold therapy, 1 with fungus infection of the lung and possibly of the liver and 1 with chronic passive congestion of the liver.

4. *Bright's Disease.* Six patients; 5 with chronic diffuse glomerulonephritis and 1 with arteriosclerotic nephritis.

5. *Upper Respiratory Infections.* Nine patients with pharyngitis, laryngitis or sinusitis.

6. *Diabetes Mellitus.* Seven patients.

7. *Miscellaneous.* Sixteen patients; 3 with thromboangiitis obliterans, 4 with carcinoma or Hodgkin's disease, 4 with hypothyroidism, 1 with non-toxic nodular goiter and 4 with neurocirculatory asthenia.

An appraisal of hepatic function was also made in each patient by the following tests: urinary excretion of galactose,^{5,7,22,23} bromsulphalein retention,²¹ and serum cholesterol partition.

The method employed to determine galactose tolerance was similar to that outlined by Althausen *et al.*⁴ with slight modifications. Following a 12 to 14 hour fast, venous blood specimens were drawn before and at intervals of 30, 60 and 120 minutes* after the oral administration of 40 gm. of galactose dissolved in 400 cc. of water. Blood glucose was removed by fermentation with Fleischmann's yeast according to the method of Somogyi.²⁴ The yeast was washed six or seven times.^{4,18} Seven cubic centimeters of a 20% yeast suspension and 2 cc. of a tungstic acid solution (Folin-Wu¹⁰) was mixed with 1 cc. of oxalated blood. The mixture was filtered and 2 cc. portions were used for the sugar determinations.† Because the reducing power of galactose is less than that of glucose, the figures obtained were increased by 24% in order to give the true value for galactose.⁴

Results. In order to conserve space the individual galactose tolerance curves are not detailed. Chart 1 shows the mean galactose tolerance curves of 24 patients over the age of 50 and 23 patients under the age of 50. Patients with hyperthyroidism, hypothyroid-

* The original technique called for 5, 15, 30, 60 and 120 minute specimens of blood.

† With the technical assistance of Anna Mei-Lan Lee, B.A.

ism, impaired liver function or Bright's disease were eliminated from this group. It will be observed that the factor of age *per se* appears to exert little influence on galactose tolerance. It should be stated, however, that the range of the highest blood galactose (2 to 92 mg. per 100 cc.) obtained in this series of "control" subjects is wider than that reported by Althausen and his coworkers (5 to 45 mg. per 100 cc.). Furthermore, 16, or 34% of the 47 patients comprising this group, showed impaired tolerance to galactose according to the standards originally described by Althausen *et al.*

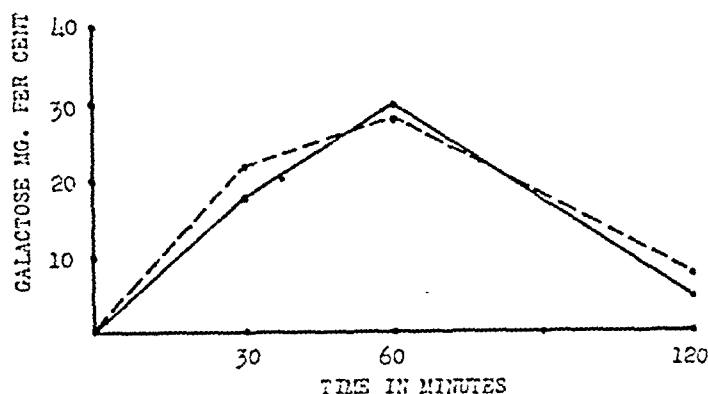


CHART 1.—The mean galactose tolerance curves of 24 patients over 50 years of age (broken line) and 23 patients under 50 years (solid line) without hyperthyroidism, hypothyroidism, impaired liver function or Bright's disease.

Chart 2 shows the average galactose tolerance curves of 20 patients with hyperthyroidism, 7 patients with impaired liver function, 6 patients with Bright's disease, 9 with upper respiratory infections and 7 with diabetes mellitus. The impaired galactose tolerance in patients with hyperthyroidism is clearly demonstrated. The range of the peak of the individual curves (17 to 136 mg. per 100 cc.) compares well with that of Althausen *et al.* (25 to 152 mg. per 100 cc.). Only 1 patient in this group showed a normal tolerance to galactose, which may be accounted for by the fact that there was marked evidence of regression of thyroid activity as indicated by sections of thyroid tissue obtained during subtotal thyroidectomy. It was further observed that there was no correlation between the basal metabolic rate and the degree of impairment of galactose tolerance. The mean galactose tolerance curve for the 7 patients with impaired liver function was moderately high. Analysis of individual curves of these patients indicated that even slight impairment of liver function without the presence of jaundice may be reflected in an abnormal curve. It is interesting to note that 4 of these patients had recently received sulfonamide therapy for lobar pneumonia and that the galactose tolerance test was carried out approximately 1 week after the cessation of the drug. Chart 2

further shows that the average galactose tolerance curves for 6 patients with Bright's disease and for 9 patients with upper respiratory infections were also moderately high. The composite curve for 7 patients with diabetes mellitus was not abnormal.

A heterogeneous group of 16 patients was also studied but the results were not included in Chart 2. Two of the 4 patients with hypothyroidism, peculiarly enough, showed impaired tolerance to galactose which was ascribed to the fact that thyroid extract was taken for its therapeutic effect. This was not unlike the abnormally high galactose tolerance curves found in normal rats fed thyroid

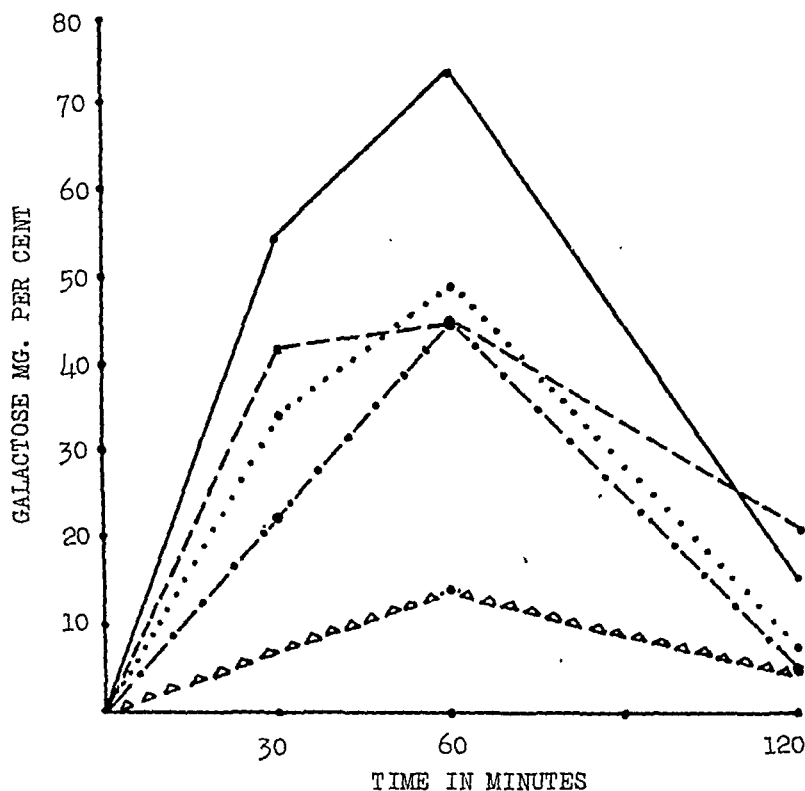


CHART 2.—The mean galactose tolerance curves of 20 patients with hyperthyroidism (solid line), 7 patients with impaired liver function (broken line), 6 patients with Bright's disease (dotted line), 9 patients with upper respiratory infections (dot and dash line) and 7 patients with diabetes mellitus (triangle line).

extract.² Four patients with neurocirculatory asthenia gave a normal response to the oral administration of galactose. This finding is important because the galactose tolerance test appears to have its greatest value in the differentiation of this syndrome from true hyperthyroidism, frequently a confusing diagnostic problem. Three patients with carcinoma and 1 with Hodgkin's disease gave abnormally high galactose tolerance curves.

Comments. The present study confirms the findings of Althausen and his coworkers^{1a, b, 3, 4} insofar as abnormally high galactose toler-

ance curves are noted in patients with hyperthyroidism. The pitfalls of this test, however, may lie in such clinical conditions as are associated with liver damage even to a slight degree and in the absence of hyperthyroidism. The presence of jaundice is known to interfere with the interpretation of this test⁴, but it is now shown that patients with Bright's disease, upper respiratory infections and possibly malignant disease may also give moderately high galactose curves. Moreover, patients who have recently received sulfonamide therapy may show impaired tolerance to galactose. It is conceivable that hepatic damage may account for the abnormal curves noted in these disorders, although the liver function tests used in this study, namely urinary excretion of galactose, bromsulphalein retention and serum cholesterol partition, did not reveal any parenchymatous liver involvement. The probability nevertheless exists that hepatic damage might have been disclosed, were more sensitive test used to detect its presence, *c. g.*, intravenous galactose tolerance⁶ and cephalin-cholesterol flocculation.^{13,20} This phase of the problem deserves further study.

Although it has frequently been demonstrated that impaired liver function is not an uncommon finding in hyperthyroidism,^{12,15} Bassett, Althausen and Coltrin⁶ believe that the impairment in galactose tolerance exhibited by thyrotoxic patients is largely due to the increased rate of absorption of this sugar from the intestinal tract and that hepatic damage when present accentuates the impairment in galactose tolerance only very little. This observation, however, is not in complete agreement with other investigators.¹⁶ Our findings indicate that in a variety of clinical conditions other than hyperthyroidism impairment in galactose tolerance exists which may be ascribed to parenchymatous liver involvement. In these conditions, however, it is conceded that the impairment in tolerance for galactose is not as great as it is in hyperthyroidism. The abnormally high galactose curves observed in thyrotoxicosis probably present a dual mechanism: inability of the liver to convert all or part of the galactose to glycogen and a rapid rate of absorption of galactose from the intestinal tracts.

Conclusions. 1. The factor of age, *per se*, appears to exert little or no influence on the galactose tolerance curve.

2. Patients with hyperthyroidism, Bright's disease, upper respiratory infections, malignant disease and those who have recently received sulfonamide therapy frequently demonstrate impairment in galactose tolerance following the oral administration of this sugar. The impairment in galactose tolerance, however, is most marked in patients with thyrotoxicosis, which may be ascribed to a dual mechanism: (a) increased rate of absorption of this sugar from the intestinal tract and (b) hepatic damage.

3. Patients with diabetes mellitus are shown to have a normal tolerance for ingested galactose.

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THE ESTROGEN-LIKE ACTION OF DESOXYCORTICOSTERONE ACETATE UPON THE ALTERED ELECTROCARDIOGRAM SEEN IN VARIOUS HYPO-OVARIAN STATES.

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AMONG a variety of commonly observed symptoms and signs in woman with ovarian dysfunction and in those undergoing a "natural" or surgical menopause, alterations of the electrocardiogram may appear, which involve chiefly the final deflection.¹¹

Relatively small doses of estrogen bring about a normalization of the electrocardiogram within a short time. Since a hypersecretion of corticotropic hormone in patients with ovarian hypofunction was assumed to be one of the causes of the vascular disturbances, and

since a close chemical relationship exists between the estrogens and the corticosterols, we have studied the effect of administration of desoxycorticosterone acetate* in a series of patients with disturbed ovarian function and altered electrocardiograms.

Case Reports. CASE 1. H. A., a woman of 27 was admitted to the hospital for palpitation, nervousness, great fatigue, and anxiety. A pan-hysterectomy had been performed 8 years previously. Two years before admission, the patient received a series of injections of an estrogenic hormone. She has been treated for "neurocirculatory asthenia."

Physical examination of the heart revealed a normal form and size, but with evidence of a marked hypermotility; the sounds were pure, and the blood pressure on admission was 120/90. There was no evidence of organic heart disease. The patient had not received digitalis or any other medicine prior to admission.

The first electrocardiogram (Fig. 1A), taken on entry to the hospital, showed a sinus rate of 85, a normal conduction time, and a slight slurring of the QRS-complexes. The T-wave in Lead I was low. In Lead II there was a depressed S-T segment followed by an almost invisible T-wave. In Lead III and in the chest lead (CR₂), the S-T segment was depressed, and the T-wave inverted. Figure 1B was taken 13 days later after the administration of 3 injections of 10,000 IU estrogen. At that time, all of the patient's symptoms had disappeared, and she was very euphoric. In the electrocardiogram the pulse rate was as before; however, the T-waves were higher in Lead I, normally positive in Lead II, and much less inverted in Lead III and the chest lead.

No medication was given for 8 days, when the patient complained again of her former symptoms and of excessive fatigue. The electrocardiogram taken at that time is reproduced in Figure 1C. The heart rate had increased to 106, the S-T segment in Lead II was again depressed, and the T-wave in that lead was lower. The inversion of the T-wave in Lead III and in the chest lead is again more pronounced. At this time 10 mg. of desoxycorticosterone acetate were given daily for 3 days. The patient again experienced a marked improvement, although she did not feel as relaxed and free from fear and fatigue as after the first series of injections. The electrocardiogram taken 5 days after that in Figure 1C (Fig. 1D) showed a marked change. There was a bradycardia of 40. The S-T segments were normal in each lead, and the T-waves were positive. One week later the patient complained of some hot flushes, pressure over the precordium, and excitability; these symptoms gradually increased. Figure 1E, taken 12 days after Figure 1D, again suggested a marked deterioration with changes which are almost like those of Figure 1C.

CASE 2. C. C., a woman of 26, was admitted for malnutrition and "hypo-ovarianism." Six years previously the patient had had an operation for oophoritis and salpingitis. Since that time her menstrual flow has lasted only 1 to 2 days and has been scanty. She had suffered from pain over the precordium, dyspnea, and palpitation. On examination, there were no signs of hyperthyroidism. The heart exhibited a normal size and form, but tachycardia and hypermotility were both present. The heart sounds were pure, and the blood pressure was 108/76. No organic cardiovascular disease existed. The patient did not receive digitalis before

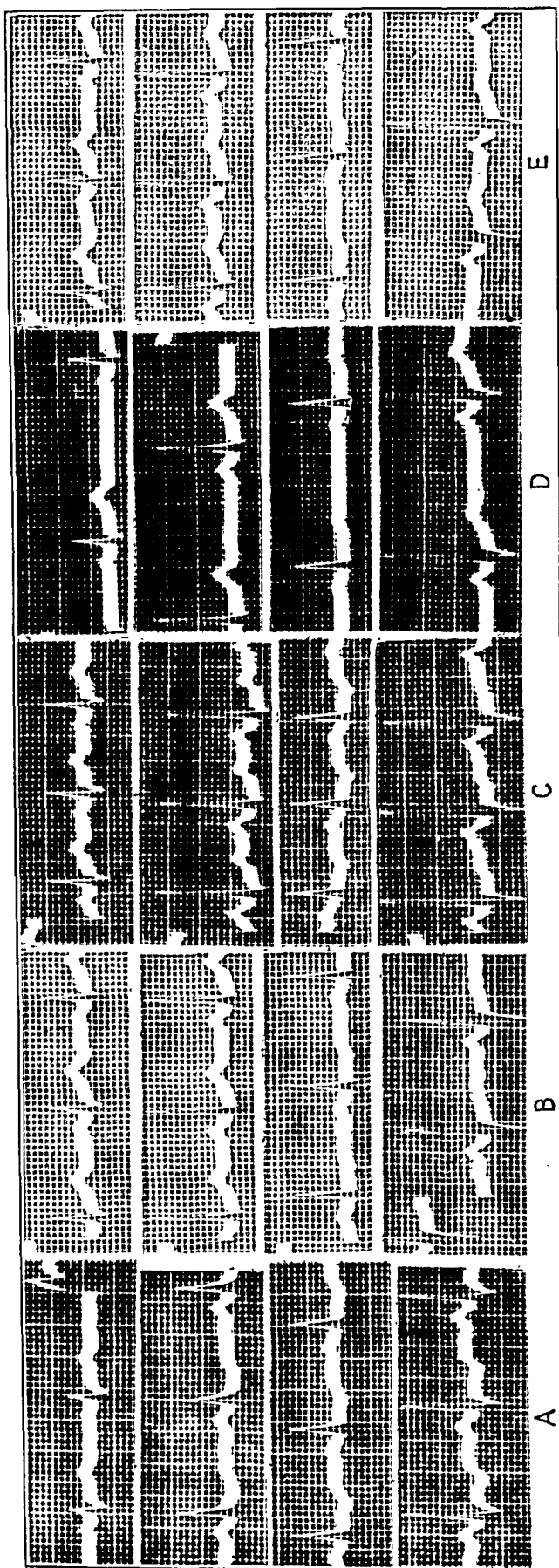


FIG. 1.—Case 1. *A* shows electrocardiogram before, and *B* following treatment with estrogenic hormone. *C* was taken 8 days later, and *D* after administration of desoxycorticosterone acetate. *E* was taken 12 days later.

each limb lead and in the chest lead (CR₂). After 5 injections of 10 mg. of desoxycortico-sterone acetate, the electrocardiogram became normal (Fig. 2*B*), and the heart rate fell to 104. The patient experienced great relief from many of her symptoms, but still believed herself to be "under high tension."

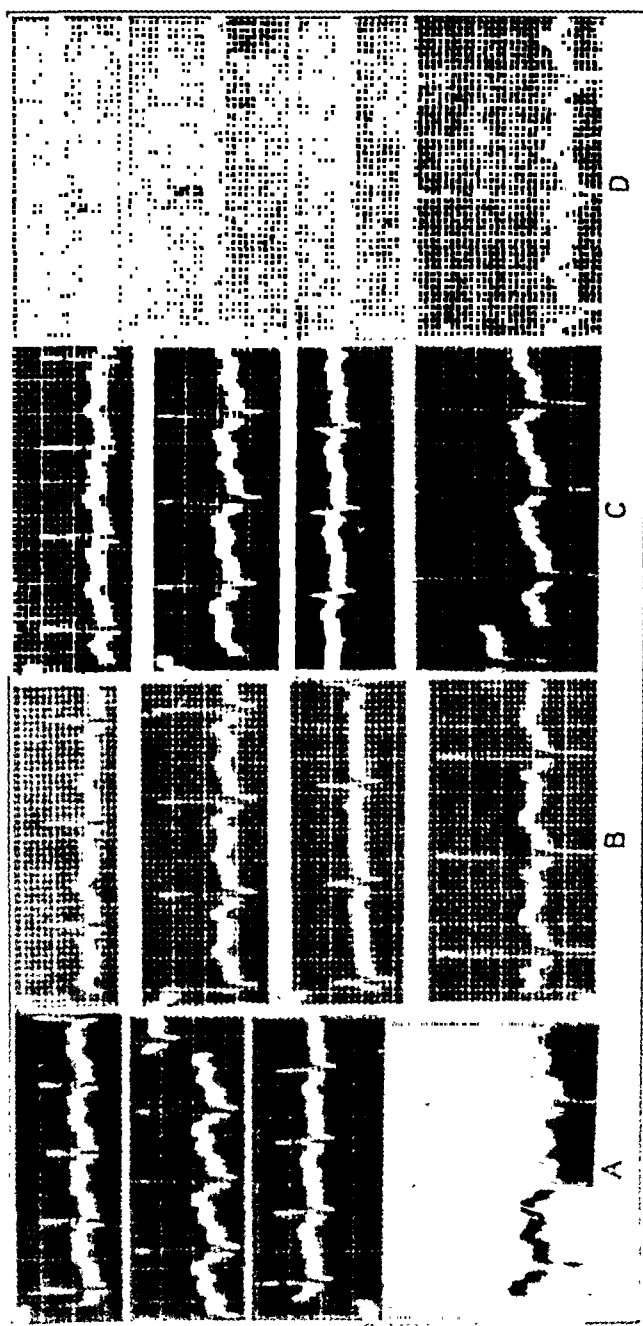


FIG. 2. Case 2. A was obtained before, and B after treatment with desoxycortico-sterone acetate. C was taken 2 months later. D was obtained after treatment with estrogenic hormone.

The next electrocardiogram (Fig. 2C) was taken 2 months after Figure 2B; no medications had been used in the interim. It showed a return of a tachycardia of 120 and a depression of the S-T segments in Leads II, III, and the chest lead. The T-wave in the chest lead had disappeared. Figure 2D was obtained 1 week after Figure 2C; in the meantime the patient had received 2 injections of 10,000 IU each of estrogenic hormone. She felt much better and showed a perfectly normal electrocardiogram.

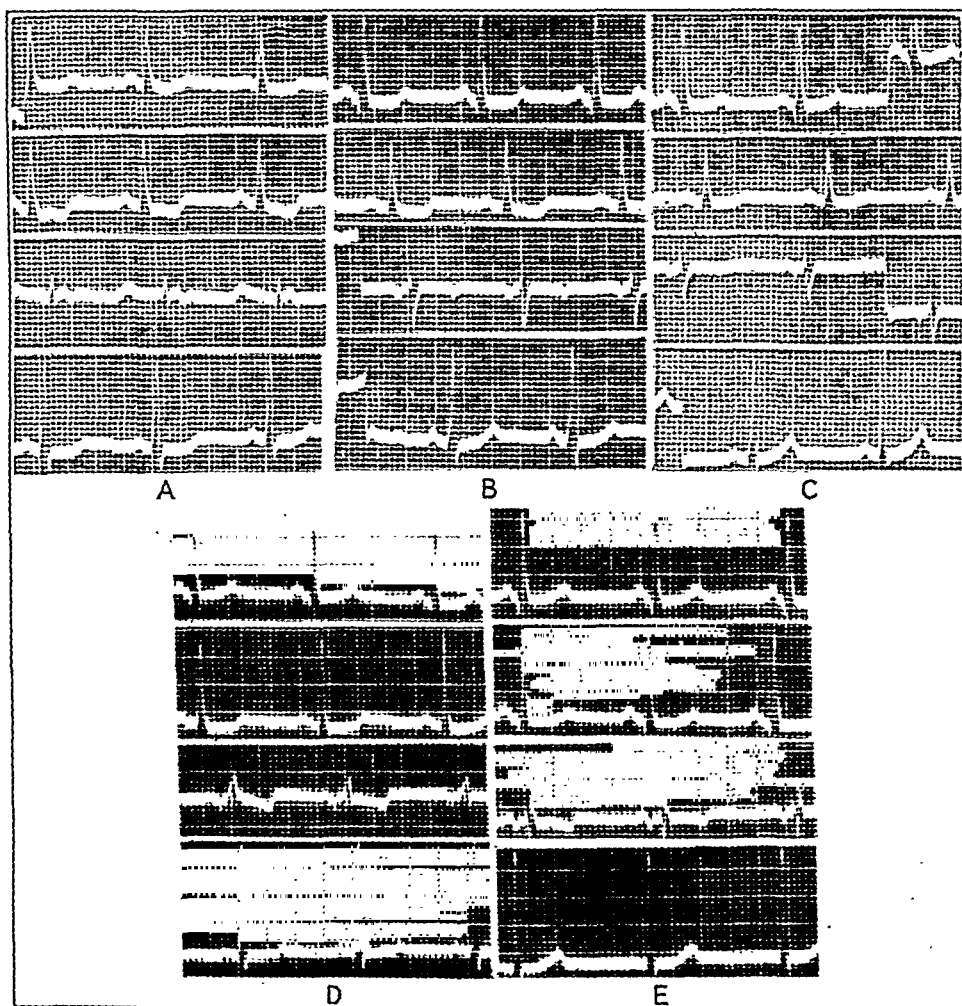


FIG. 3.—Case 3. A was taken before, and B after injections of desoxycorticosterone acetate. C was made after treatment with estrogen; D was obtained 8 months later, and E was obtained after treatment with desoxycorticosterone acetate.

CASE 3. K. C., a woman of 47, was readmitted to the hospital 4 weeks after an operation for prolapsus uteri. She complained of precordial pain, dyspnea, and flushes. Physical examination did not reveal any signs of an organic heart lesion. The slightly obese patient had a heart which was normal in size and form. The second aortic sound was slightly accentuated, the heart sounds were pure, and the blood pressure was 100/60, and the blood Wassermann test was negative. The patient did not receive digitalis before admission, and there were no abnormal findings besides uterine fibroids.

The first electrocardiogram, taken on admission (Fig. 3A), showed a regular sinus rhythm with a marked depression of the S-T segment, especially in Lead II and in the chest lead. The T-waves were abnormally low. Figure 3B was taken 1 week later after injection of 10 mg. of desoxycorticosterone acetate daily for 4 days. There was a marked improvement, the depression of the S-T segments had diminished, and the T-waves became positive. A series of 7 injections of 2000 RU estrogen caused a complete normalization of the electrocardiogram (Fig. 3C, obtained 10 days later.)

The patient was reexamined 8 months later, at which time hot flushes, palpitation, and so forth, were again present. The electrocardiogram (Fig. 3D) showed a normal Lead I, but an abnormal S-T segment and an abnormal T-wave in Lead II and the chest lead. A series of 6 injections of 10 mg. of desoxycorticosterone acetate administered twice weekly caused a complete disappearance of these changes with normalization of the electrocardiogram and marked improvement in subjective symptoms.

CASE 4. E. F., a woman of 47, seen through the courtesy of Dr. George Lutton, was admitted to the hospital because of weakness, loss of weight, palpitation, tachycardia, nervousness, dizziness, and insomnia. These symptoms had begun several months after a supravaginal hysterectomy 3 years previously, at which time, however, neither tube nor ovaries were disturbed. These manifestations had become increasingly severe to the time of admission. No digitalis had been given within the 6 months immediately preceding her hospitalization.

Physical examination revealed a well-nourished, well-developed woman with normally pigmented skin, heart well within normal limits of size, sounds pure, and blood pressure of 120/70. There was no evidence of organic disease in the heart or elsewhere.

The first electrocardiogram showed a sinus rate of 116 and a normal conduction time. There was a depression of the S-T segment in all three limb leads, the T-wave in Lead II was inverted, and the T-wave in CR₁ was biphasic. The next electrocardiogram (Fig. 4B) was taken 7 days later after 6 daily injections of 5 mg. of desoxycorticosterone acetate. The rate was 98, and the conduction time shortened to 0.18 sec. The S-T segment in all leads was less depressed than before, and the T-wave in Lead II was low but positive. The third tracing (Fig. 4C) was made 2 days later after 2 10-mg. doses of desoxycorticosterone acetate. The T-wave in Leads I and II and in CR₁ was then normal. The last electrocardiogram (Fig. 4D) was recorded 1 week after the preceding, during which time no medication had been given. No variation from Figure 4C was observed.

Under treatment, all of the patient's symptoms disappeared, her strength increased, and the nervousness, insomnia, and mental depression which were so prominent on admission had completely ceased to disturb her. One week after discharge from the hospital, during which time she received no medication, she was placed upon estrogenic hormone therapy, and while opportunity has not been afforded for further examination, reports from her physician indicate that she remains symptom free.

CASE 5. G. S., a woman of 21, was admitted to the hospital complaining of acute right lower quadrant pain, shifting myalgic and arthralgic pains in the arms and legs, and palpitation. The patient was small and frail, suggesting the generally hypoplastic type, although she was well proportioned with normally developed secondary sex characteristics. Her menses began at age 14 and were accustomed to recur at 33- to 45-day intervals, with 2 to 4 days of flow, the flow being scanty except for the first and sometimes the second day. Her right lower quadrant pain was at first ascribed to an appendiceal involvement, but was later thought to be of ovarian origin; no operation was performed.

Her first electrocardiogram (Fig. 5A) was taken after 12 days of complete

bed rest. The rate was 106. The P-R interval was 0.12 sec. The S-T segments were depressed in Leads I and II, and the T-waves were abnormally low in Lead II. In Lead III, the T-wave was inverted. The chest

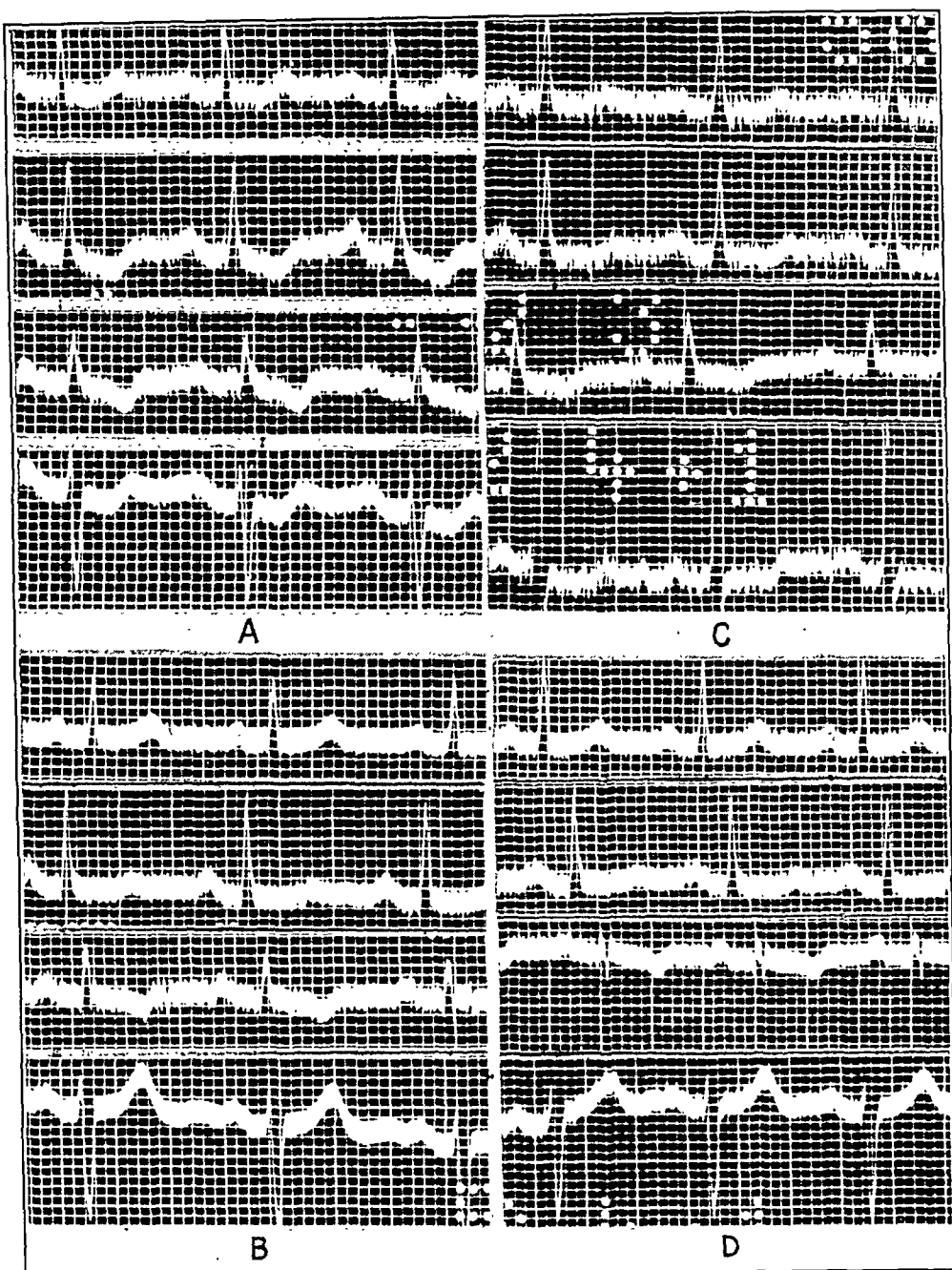


FIG. 4.—Case 4. *A* was taken before *B* after administration of desoxycorticosterone acetate. *C* was obtained after continuation of this treatment with an increased dose; *D* was taken 1 week later.

lead (CF_4) was normal. After the administration of desoxycorticosterone acetate, 5 mg. daily for 11 consecutive days, a second electrocardiogram was made (Fig. 5*B*), which showed less depression of the S-T segments and

higher T-waves than formerly. Desoxycorticosterone acetate was continued in the same dose for an additional 11 days when a third tracing was obtained (Fig. 5C), in which practically normal S-T segments and T-waves existed. No further treatment was given for 13 days, when the electrocardiogram revealed changes noted in Figure 5D. The T-wave in Lead I

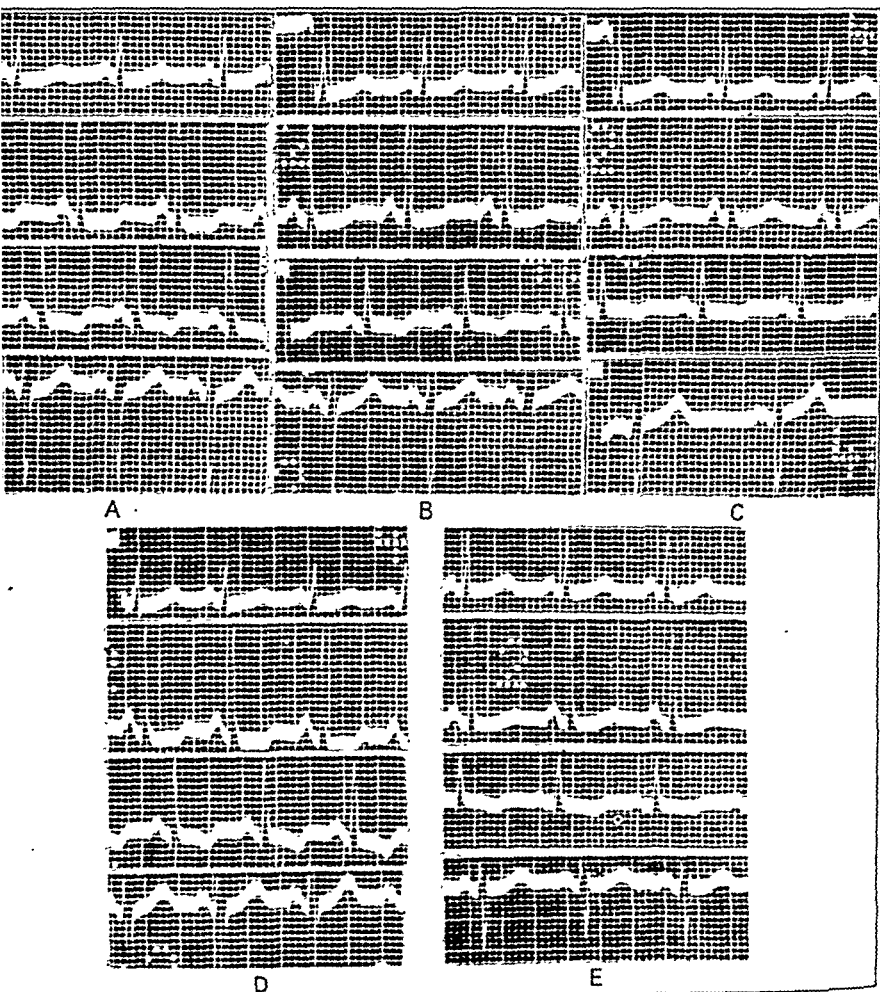


FIG. 5.—Case 5. *A* shows the electrocardiogram before, *B* after treatment with desoxycorticosterone acetate; *C* was obtained after continuation of this treatment. *D* was registered 13 days later. *E* was obtained after treatment with estrogenic hormone.

was lowered with a slight depression of the S-T segment; the S-T segment in Lead II was markedly depressed with a low deflection of the T-wave above the iso-electric line. The T-wave in Lead III was more deeply inverted than at the time of the first tracing, and the S-T in Lead CF₄ was slightly depressed. The heart rate was 115.

One week later, pregnant mare's serum (100 units, Cole and Saunders) were administered, and this dose was repeated every second day for 6 injections. Immediately following the fourth such treatment, estrogenic hormone, 10,000 international units, was given daily for 5 days. On the sixth day, an electrocardiographic tracing was made (Fig. 5E), which shows again changes in the direction of normal. The T-wave in Lead I is higher, and the depression of the S-T segment in Lead II is markedly diminished.

CASE 6. C. G. was admitted to the hospital for menorrhagia. The 43-year-old colored woman had had prolonged menstrual periods for the past 4 years. She was admitted to the gynecologic ward where uterine fibroids were discovered. Because of swelling of the ankles and hands, it was decided to treat her conservatively, and she was transferred to the medical ward.

Examination revealed a heart of normal size and form with a soft systolic murmur over the base. The blood pressure was 170/124. There was no evidence of an aortitis although the Wassermann reaction was 4+. All other laboratory findings were normal; there was no anemia and no evidence of congestion.

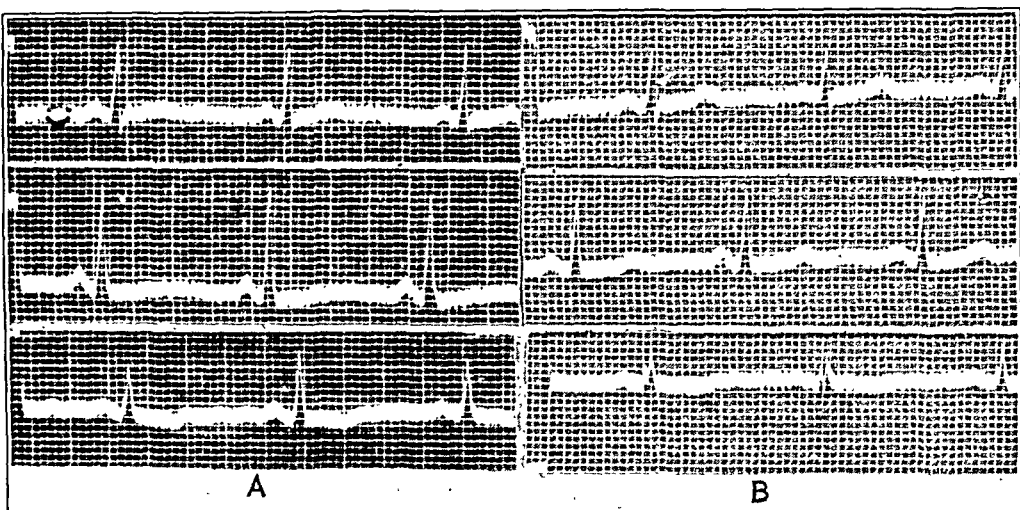


FIG. 6.—Case 6. A shows the electrocardiogram before, and B after administration of desoxycorticosterone acetate.

The electrocardiogram (Fig. 6A) showed a normal sinus rhythm with a normal conduction time. The T-waves in Lead I were abnormally low and were almost invisible in Lead II. Following 5 daily injections of 10 mg. of desoxycorticosterone acetate, the T-waves became completely normal (Fig. 6B). The blood pressure fell to 132/88, and the patient was dismissed without any symptoms. At no time had the patient received digitalis.

Discussion. The clinical findings in each of the 6 cases whose electrocardiographic findings are detailed above were unequivocally those of disturbed ovarian function. Three of these patients were of menopausal age, 2 had undergone surgical castration, and one was of a constitutionally inferior type associated with frank signs of gonadal insufficiency.

In 4 of the cases, the effect on the electrocardiogram of both desoxycorticosterone acetate and estrogenic hormone was shown to

be identical in kind, varying only in degree with the size of the dosages employed. In the fourth and sixth patients, desoxycorticosterone acetate alone was used. Improvement in the clinical symptoms followed the administration of desoxycorticosterone acetate as well as the use of the ovarian hormone. However, relief of symptoms was much more profound under estrogenic hormone therapy than it was under treatment with the adreno-cortical steroid.

The duration of improvement both in the clinical condition and in the electrocardiographic tracings varies greatly from individual to individual. As in Case 1, many patients will relapse in from 7 to 10 days after the cessation of therapy. We have followed such individuals for as long as 4 years, during which time continuous treatment has been necessary to control symptoms and electrocardiographic changes. Some patients, particularly those in the climacterium, appear to be more or less permanently relieved of circulatory and other disturbances by from one to several doses of either estrogenic or adreno-cortical steroid.

The action of desoxycorticosterone acetate in connection with ovarian dysfunction appears to have some degree of specificity. We have administered 10 mg. of desoxycorticosterone acetate for 14 days to a patient with hypopituitarism and polyglandular manifestations without any influence whatsoever on the inverted T-waves of his electrocardiogram. Again, no change following the use of similar amounts of desoxycorticosterone acetate has been noted in the inverted T-waves in Leads I and II of the electrocardiograms of patients with hypertension and evidence of left ventricular strain. According to Raab,⁶ overdosage with cortico-steroid may cause changes in the electrocardiogram indicative of anoxia.

A satisfactory explanation of the ability of estrogens and desoxycorticosterone acetate to return the altered electrocardiogram to normal is fraught with some difficulties. From previous studies with the ovarian hormone, it was suggested that the vasodilating and electrolyte regulating actions of the ovarian hormone were probably responsible.¹¹ In view of the fact that the predominant influence of desoxycorticosterone acetate on blood-vessels is one of vasoconstriction, the vasodilation hypothesis becomes now much more difficult to defend. The effect might be an indirect one upon the ovary by way of the hypophysis, as it is known that cortical steroids do produce changes particularly in the basophile cells. This would, however, not explain the return to normal of the electrocardiogram of the two castrate patients.

Changes in calcium metabolism may play a part in the observed action, but while a number of observers are agreed upon the presence of changes in calcium metabolism in relation to the ovarian cycle in many of the lower animals,^{7,17} such changes are not easily perceived in the human being^{5,17} and even less well evaluated.

That sex and adreno-cortical hormones alike have a definite influence upon electrolyte and water metabolism and balance seems to be proved beyond reasonable doubt.^{15,16} Thorn and Engel demonstrated that adreno-cortical hormones, desoxycorticosterone acetate among them, and the sex hormones, while differing markedly from each other in the potency and duration of their effects, all showed in common an ability to decrease the renal excretion of sodium and chloride and to raise the excretion of potassium. It is known that potassium and glycogen move into and out of muscle cells together,^{1,8,10} and that the action of potassium on the heart is to some extent a specific one not shared by other skeletal muscles generally. Schumann determined the glycogen and creatine phosphate content of the heart of the male rat before and after castration and following the administration of synthetic male sex hormone.¹² After castration the amount of creatine phosphate diminished to 63% of normal, and the glycogen to 66% of normal. Administration of male sex hormone to the castrated animal augmented the amount of glycogen to 162% and returned the creatine phosphate to pre-castration levels. The giving of sex hormone to the normal animal increased the quantity of glycogen in the heart by approximately 100%.

The influence of desoxycorticosterone acetate on the electrocardiographic changes seen at the menopause and in other hypovarian states is in part explained by what is thus far known of its gynecogenic action.³ The progesterone-like activity of desoxycorticosterone acetate has been repeatedly observed and described following the use of proper dosages and conditions of application,^{2,4,13,14} but may fail to appear when they are not present.^{2,13,14} Attention should also be called to its direct estrogenic effect upon the vaginal mucous membrane of postmenopausal women.⁹

In conclusion, it is safe to assert that desoxycorticosterone acetate returns to normal the altered electrocardiograms occasionally observed in women with ovarian insufficiency in a similar way as ovarian follicular hormone. The manner in which this effect is brought about is far from settled. A vascular action, a regulatory influence upon blood and tissue electrolytes, and an interhormonal response must all be considered among the primary causes giving rise to secondary changes in the nutritional state and functional capacity of the heart.

Summary. 1. Six women with clinical manifestations of hypovarianism and electrocardiographic changes, typical of such a state have been described.

2. The influence of desoxycorticosterone acetate and ovarian follicular hormone on the clinical and electrocardiographic disturbances present in each of 4 of these has been recorded and evaluated. In 2 additional individuals, changes following the administration of desoxycorticosterone acetate have been noted.

3. In each of the 4 patients to whom administered, estrogens returned the previously altered electrocardiogram to normal. Total dosages necessary for this effect varied from 14,000 to 50,000 international units.

4. In all 6 patients, the previously altered electrocardiogram reverted to normal under the influence of desoxycorticosterone acetate in total doses of 30 mg. to 60 mg. The response was equivalent in kind and in degree to that observed following the administration of ovarian follicular hormone, provided proper dosages were employed.

5. Possible explanations of this action of desoxycorticosterone acetate upon the heart are discussed. Among these we must include a direct action by way of the blood-vessels and blood and tissue electrolytes, and an indirect action by way of other endocrine glands, notably the pituitary and the gonads.

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STUDIES ON CONGESTIVE HEART FAILURE.

II. IMPAIRED RENAL EXCRETION OF SODIUM CHLORIDE.

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THE ions which predominate in the edema fluid of cardiac failure are sodium and chloride. A diet low in salt may prevent formation of edema in patients with heart failure,⁷ whereas the administration of sodium salts results in oliguria and increase in weight.

These considerations indicate that retention of sodium and

chloride is involved in the accumulation of edema in patients with heart failure. The mechanism of this retention is unknown. We have attempted to ascertain whether it lies in the kidneys.

Procedure. An abundant supply of sodium and chloride was provided the kidneys of 5 patients with congestive heart failure by maintaining the concentrations of these ions in the blood at abnormally high levels for several hours following an intravenous injection of hypertonic sodium chloride solution. To prevent lowering of the serum sodium and chloride levels by dilution, an attempt was made to reestablish cardiac compensation before the test period, in order that extracellular fluid be minimized; and ingestion of fluid was denied for 24 hours following the injection. The renal excretion of sodium and chloride was measured, and compared to the excretion in 2 subjects without heart disease who were given a similar stimulus. For at least 2 weeks preceding the experiment all subjects, including the 2 without heart disease, were maintained on a diet containing 1 gm. of sodium chloride daily, calculated from sodium content estimated from standard food tables; 2000 calories were provided, apportioned from approximately 180 gm. of carbohydrate, 65 gm. of protein and 115 gm. of fat. The daily intake of fluid was maintained at either 1500 or 2000 cc. The output of urine, the urinary excretion of chloride, and the body weight (before the ingestion of food or fluids) were measured daily. All patients with congestive heart failure save S. DiM. had received at least 1 injection of a mercurial diuretic during the month preceding the experiments, but this measure was not employed within 2 weeks of the test. Xanthine diuretics were not used for the preceding 2 months except as indicated in Figure 1. Each of the 5 subjects with heart failure was taking digitalis at the time of the experiment. Edema, if present, was minimal. All subjects remained in bed during the first 24 hours of the experiment; only M. H. remained in bed throughout the test.

An outline of the experiment follows: *Day 1* (hours, 0 to 24): All liquids were withheld for 24 hours; the diet was deficient in fluids and contained the usual 1 gm. of salt. At time 0 hours, 400 cc. of 6% solution of sodium chloride, containing 24 gm., was injected intravenously over the course of 30 minutes. Urine was collected in 2- to 6-hour periods. Each specimen was analyzed for chloride, and in some cases for sodium and urea-plus-ammonia nitrogen (Table 2). Venous blood was usually collected at times 0, 1, and approximately 8 hours for estimation of serum chloride, and in some cases serum sodium and carbon dioxide content and blood urea nitrogen (Table 1). Venous pressure was also measured. *Day 2* (hours 24 to 48): Liquids were administered as before the test (1500 to 2000 cc.), and the diet was as usual. Urine was collected either as on Day 1, or as a pooled 24-hour specimen. A blood sample was taken at time 24 hours, previous to ingestion of food or fluids. The analyses performed on blood and urine were the same as on Day 1. *Day 3 and after:* Same as Day 2.

As noted above, the usual procedure was to administer 24 gm. of sodium chloride in a single intravenous injection of 6% solution at time 0 hours. However, M. M. received a single injection of 21 gm. only, J. B. 15 gm. (250 cc.) at time 0 hours and an additional 9 gm. (150 cc.) at time 6 hours, and M. H. 24 gm. at time 0 hours and 9 gm. at time 8 hours. During the administration of the 6% solution of sodium chloride several of the subjects complained of headache and nausea. For a few hours following the injection the patients W. D. and M. H., with severe congestive failure, exhibited orthopnea and dyspnea, and râles were heard in the lungs. All of the patients complained of thirst; 2 were allowed a few cubic centimeters of crushed ice during the first day. Albuminuria, when present previous to the injection of salt, was not increased by it. A week or more

after the experiment a mercurial diuretic was given to all the patients with cardiac failure, except in the case of the first period of N. J., when abdominal paracentesis was performed, in order to free them of edema accumulated during the test.

TABLE 1.—VENOUS PRESSURE AND CHEMICAL ANALYSES ON BLOOD BEFORE AND AFTER INTRAVENOUS INFUSION OF SODIUM CHLORIDE (21 TO 33 GRAMS).

Subject, date, diagnosis.	Time after injection of salt (hrs.).	Serum sodium (m.eq. per liter).	Serum chloride (m.eq. per liter).	Serum carbon dioxide content (mM. per liter).	Blood urea nitrogen (mg. per 100 cc.).	Venous pressure (mm.).
Case 1 (G. S.) January, 1940 Bronchial asthma	0 1 10 24 48 120	97 116 114 111 105 100	60
Case 2 (M. M.) October, 1940 Hypoproteinemia	0 1 12 24 48 72 120	142 153 150 151 144	108 119 119 117 112 109 107	16.5 15.6 21.1 18.8	105 105 94 111
Case 3 (S. DiM.) February, 1940 Mild heart failure	0 8 24 72	97 113 111 100	127
Case 4 (W. D.) June, 1940 Severe heart failure	0 1 9 24 72	136 151 148 149 137	98 111 109 108 97	225
February, 1941	0 1 9 24 48	136 146 143 146 144	97 107 107 109 104	18.3 .. 18.6 19.3 21.6	205 210 221 198 220
Case 5 (M. H.) June, 1941 Severe heart failure	0 1 9* 24 48 72 120	137 148 153* 155 150 143 137	94 111 118* 117 110 106 103	33.1 29.8 27.0* 29.6 30.6 28.3 29.2	6.2 8.6 9.2 9.1 ..	125 95 175 150 172 172
Case 6 (J. B.) November, 1940 Severe heart failure	0 6 9* 24 72 96 168	107 109 115* 112 105 103 103	115 167 158 193
Case 7 (N. J.) January, 1940 Severe heart failure; renal disease	0 1 24 96 192	99 112 107 103 100	245
March, 1940	0 1 9 24 48 120	97 111 111 112 110 101	61

* Following second injection of 6% sodium chloride; see text under "Procedure."

Analytical Methods. Serum chloride was estimated by the method of Van Slyke.^{3a}† The Volhard-Arnold procedure⁴ was used to measure urinary

† The normal values obtained by this method range from 99 to 108 milliequivalents per liter (average about 102). The chloride content of the serum of patients taking such salt-poor diets was usually found to be lower than this; 96 to 100 milliequivalents. The initial values of 1 control and all but 2 cardiac patients were in this range; the other control and 1 cardiac exhibited high initial values.

chloride, with occasional checks by the titrimetric silver iodate method of Sendroy.⁸ Urinary sodium was estimated by the technique of Butler and Tuthill,¹ as described for urines of "ordinary sodium content." Butler and Tuthill's method, modified by Consolazio and Dill,² was also used for the measurement of serum sodium. Whole blood and urine were analyzed for

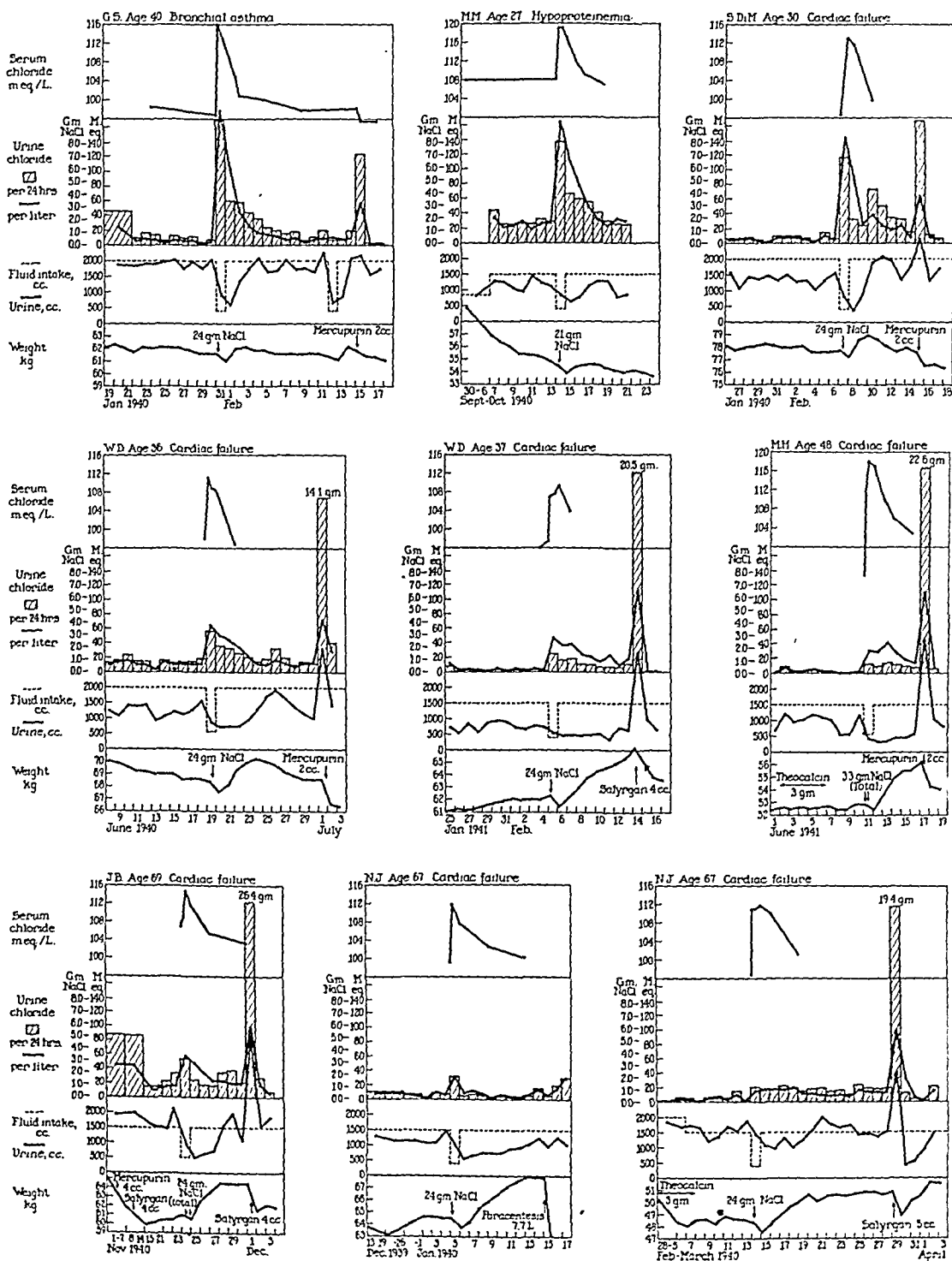


FIG. 1.—Data on all patients studied.

TABLE 2.—URINARY EXCRETION OF UREA, SODIUM AND CHLORIDE, AND UREA CLEARANCE FOLLOWING INTRAVENOUS INFUSION OF SODIUM CHLORIDE (21 TO 33 GRAMS).

Subject, date, diagnosis.	Time after injection of salt (hrs.: min.).	Volume of urine for period (cc).	Sodium concentration (m.eq. per liter).	Chloride concentration (m.eq. per liter).	Sodium content (m.eq. per specimen).	Chloride content (m.eq. per specimen).	Urea-plus-ammonia nitrogen (mg. %).	Urea-plus-ammonia clearance (% of normal).
CASE 1 (G. S.)								
January, 1910	0:00-0:50	110	..	31.1	..	3.4
Bronchial asthma	0:50-6:58	296	..	178.9	..	53.0
	6:58-13:01	198	..	172.1	..	34.1
	13:01-19:00	120	..	191.8	..	23.0
	19:00-21:00	204	..	272.1	..	55.5
	0:00-21:00	928	..	182.1	..	169.0
	21:00-48:00	592	..	162.9	..	60.9
CASE 2 (M. M.)								
October, 1940	0:00-4:20	1120*	<20.0	25.6	..	28.7	..	88.6*
Hypoprotecinemia	4:20-6:15	302	173.3	207.8	52.3	62.7	520	60.2
	6:15-9:15	44	121.5	140.2	5.3	6.8	1245	95.8
	9:15-13:01	63	93.8	154.9	5.9	8.8	1411	76.8
	13:01-18:48	128	136.2	146.0	17.4	18.7	1385	95.8
	18:48-24:00	190	180.4	139.5	34.3	24.8	1348	91.7
	0:00-24:00	114	171.6	142.6	19.6	16.3	1462	91.4
	24:00-48:00	841	160.2	164.3	134.8	138.1	..	85.3
		605	110.1	169.6	66.6	66.3	..	110.5
CASE 3 (S. DiML)								
February, 1910	0:00-4:11	200	..	112.9	..	22.6
Mild heart failure	4:11-10:09	275	..	128.1	..	35.2
	10:09-16:11	180	..	164.2	..	29.6
	16:11-22:11	125	..	173.8	..	21.7
	22:11-24:00	36	..	156.7	..	5.6
	0:00-24:00	816	..	110.5	..	114.7
	24:00-48:00	372	..	37.4	..	32.5
CASE 4 (W. D.)								
June, 1910	0:00-5:56	410	56.5	70.6	23.2	28.9
Severe heart failure	5:56-12:00	210	41.9	59.0	8.8	12.4
	12:00-18:00	138	57.7	51.3	8.0	7.1
	18:00-24:00	134	39.6	58.1	5.3	7.8
	0:00-24:00	892	60.8	63.0	45.3	56.2
	24:00-48:00	715	38.7	51.3	37.7	36.7
February, 1911								
	0:00-3:54	710*	<20.0	2.7	..	1.9	..	84*
	3:54-5:33	152	53.6	79.0	8.2	12.0	862	73
	5:33-11:01	62	<20.0	29.2	<1.2	1.8	1171	91
	11:01-16:29	95	22.0	31.0	2.1	2.9	1333	73
	16:29-24:00	112	29.4	29.2	3.3	3.3	1464	86
	0:00-24:00	118	21.6	44.8	2.6	5.3	1436	72
	24:00-48:00	539	<22.8	46.9	<17.4	25.4	..	77
		452	<20.0	36.7	<9.0	16.6	..	77

[illegible]

* Average clearance and total urine volume for 24 hours preceding infusion.
† Second injection of 6% sodium chloride administered during this period; see text under "Procedure."
‡ Mercaptopurin, 2 cc. administered intravenously this day.

urea-plus-ammonia nitrogen by the method of Van Slyke and Kugel,^{9,10} and the urea-plus-ammonia clearance was calculated from these data by the formulæ of Møller, McIntosh, and Van Slyke,⁶ correcting urine flow for size on the basis of height.⁵ Serum carbon dioxide content was measured by the method of Van Slyke and Neill.¹¹ Venous pressure was measured by the direct method and is expressed as millimeters of 0.8% solution of sodium chloride; heart level was assumed to be 5 cm. below the sternomanubrial junction, with the patient in the supine position.

Case Reports. The 2 control subjects, G. S. and M. M. (Cases 1 and 2) suffered from bronchial asthma and hypoproteinemia respectively; the renal function of neither was impaired. G. S. was chosen as a relatively normal individual; M. M. because of the presence of edema not due to cardiac or renal diseases. Of the 5 patients with heart disease, 3 (S. DiM., W. D. and M. H., Cases 3, 4 and 5) had rheumatic heart disease with no impairment of renal function and no evidence of active rheumatic fever. Two patients (J. B. and N. J., Cases 6 and 7) had arteriosclerotic heart disease; there was evidence of impairment of renal function in the latter.

CASE 1.—G. S., male, age 40, height 175 cm., had suffered from mild bronchial asthma, unaccompanied by cardiovascular or renal complications. Urea clearance was 80% of normal.

CASE 2.—M. M., female, age 29, height 157 cm., had moderate anasarca due to hypoproteinemia, possibly complicating sprue. The edema was of 11 years' duration and had responded in the past to mercurial diuretics. Plasma albumin concentration was 1.8 and globulin 1.6 gm. per 100 cc. Her serum chloride concentration previous to the test was always higher than normal, ranging from 107 to 110 m.eq. per liter, and her serum carbon dioxide content was 26.4 mM. per liter. There was no evidence of cardiac or renal lesions. The urea clearance averaged 100% of normal. The urine contained no protein or formed elements, and had a maximum specific gravity of 1.026. Minimal edema was present at the time of her test, which was performed at a time when, apparently in association with the recent institution of the low salt diet, a diuresis was in progress.

CASE 3.—S. DiM., female, age 30, height 157 cm., suffered from rheumatic heart disease with mitral stenosis. She had complained of exertional dyspnea and slight edema intermittently for 3 years. Her blood pressure was 130/80. Urea clearance was 90% of normal, and the maximum urinary specific gravity 1.026. There was no evidence of heart failure at the time of her test.

CASE 4.—W. D., male, age 42, height 166 cm., suffered from rheumatic heart disease, with mitral stenosis, aortic insufficiency, and auricular fibrillation. Symptoms and signs of severe congestive failure appeared 1 year before the test of June, 1940. Blood pressure was 160/80 in June, 1940, and 140/70 in February, 1941. There was slight albuminuria (1+). In May, 1940, the plasma albumin measured 3.3 and the globulin 3 gm. per 100 cc.; in April, 1941, these figures were 4.1 gm. and 2.9. The urea clearance averaged 90% of normal; and the maximum urinary specific gravity in June, 1941, was 1.024. Even with rest and diuretics edema was not completely controlled. Slight jaundice was frequently observed. At the time of each of the two tests performed on this patient, in June, 1940, and February, 1941, slight ascites, enlargement of the liver and orthopnea were noted, decompensation being more marked when the first was done.

CASE 5.—M. H., female, age 48, height 154 cm., suffered from rheumatic heart disease, with auricular fibrillation, mitral stenosis, and tricuspid insufficiency. Menopause occurred 5 years before admission. She had noted symptoms and signs of heart failure for 12 years, and edema, not satisfactorily controlled by digitalis or mercurial diuretics, was constant for 5 years. Blood pressure was 132/80. The urine contained albumin

(1+). The maximum specific gravity of the urine was 1.024. The plasma albumin concentration was 3.9 and the globulin 3 gm. per 100 cc. Slight orthopnea persisted at the time of the test, there was a small hydrothorax, and her liver was enlarged.

CASE 6.—J. B., male, age 69, height 165 cm., suffered from arteriosclerotic heart disease, with auricular fibrillation. Symptoms of severe congestive failure had been present for 3 years. Blood pressure was 132/84. The urine contained albumin (2+) and a few red blood cells. The plasma albumin was 3.6 and the globulin 2.8 gm. per 100 cc. The blood non-protein nitrogen was 32 mg. per 100 cc.; the urea clearance, measured 2 years before the test, was 70% of normal, the maximum specific gravity of the urine was not determined. Despite use of diuretics, orthopnea and edema were observed at times in the hospital. There was no edema at the time of his test, but his liver was enlarged.

CASE 7.—N. J., male, age 67, height 160 cm., suffered from arteriosclerotic heart disease with aortic insufficiency and auricular fibrillation. Symptoms and signs of severe congestive failure had been present for 3 years. Blood pressure was 142/80. The plasma albumin in July, 1940, was 3.7 and the globulin 3.2 gm. per 100 cc. Urine contained albumin (1+). The urea clearance was 37% of normal in October, 1939, and again in February, 1940; the blood urea nitrogen on these occasions was 23 and 27 mg. per 100 cc. Edema was difficult to control. Ascites and edema were present at the time of the first test performed; compensation had been partially restored at the time of the second. The patient died in uremia in January, 1941. At autopsy the kidneys showed only moderate arteriosclerotic changes.

Results. During the 24 hours following the injection of salt, the renal excretion of sodium and chloride ions in the 4 patients with severe cardiac disease was not more than 30% of that observed in the 2 control subjects. In respect to chloride the urine of the patients with severe heart disease was always hypotonic when compared with the serum.

The changes in the concentrations of chloride and sodium in the serum are described in Table 1. The degree of elevation produced varied from subject to subject; however, 24 hours after the injection the serum chloride and, when determined, sodium concentrations in all subjects proved to be at levels higher than normal.

The urinary excretion of these ions, and the urea clearance values, are given in Table 2. More extended data on urinary chloride are presented in the graphic analyses (Fig. 1). The 2 control subjects (Cases 1 and 2) achieved urinary chloride concentrations of 182 and 164 m.eq. per liter during the 24 hours following the injection of salt; the total 24-hour excretion of chloride was 169 and 138 m.eq. Thus, hypoproteinemia of a degree sufficient to cause edema did not prevent Case 2 from excreting salt approximately as efficiently as did the other control subject, Case 1. The patient convalescent from mild cardiac failure (Case 3) achieved a concentration of 140 m.eq. of chloride per liter, and excreted 115 m.eq. in 24 hours. The three tests on the 2 patients recovering from severe cardiac failure who exhibited normal or elevated urea clearance (Cases 4 and 5) revealed 24-hour chloride concentrations of 63, 47 and 30 m.eq. per liter; the total 24-hour outputs of chloride were

56, 25 and 12 m.eq. Case 6, the patient recovering from severe heart failure whose renal function was not recently investigated, excreted chloride in a concentration of 58 m.eq. per liter, the 24-hour output of chloride being 55 m.eq. Finally, Case 7, who, in addition to suffering from severe cardiac disease showed evidence of impaired renal function, on 2 different occasions excreted chloride in a concentration of 31 and 14 m.eq. per liter; the total 24-hour outputs were 32 and 21 m.eq. The concentration of sodium in the urine of the patients in whom the measurement was made paralleled that of chloride.

Chloride clearances were calculated from the data presented in Tables 1 and 2 and from additional data not included therein. For a given subject, there was noted a tendency for the clearance to vary directly with the serum chloride level and the urine volume. There were numerous marked deviations from these trends, however, particularly in the patients with heart disease. The averages of the chloride clearances* for each patient during those periods when the falling curve of the serum chloride level was in the range 108 to 111 m.eq. per liter inclusive follow: Case 1, 0.93 cc. of serum per minute; Case 2, 0.40 cc.; Case 3, 0.47 cc.; Case 4 (June, 1940), 0.24 cc.; Case 4 (February, 1941), 0.13 cc.; Case 5, 0.11 cc.; Case 6, 0.20 cc.; Case 7 (January, 1940), 0.16 cc.; and Case 7 (March, 1940), 0.15 cc. of serum per minute. Case 5 whose chloride clearance throughout the test was the lowest observed in any of the patients also showed the lowest urine flow.

The administration of mercurial diuretics to patients with cardiac failure may occasion excretion of sodium and chloride in concentrations exceeding those observed following the intravenous administration of sodium chloride; this fact is demonstrated by the data on Cases 4, 5, 6 and 7, presented in Table 2 and Figure 1. For example, Case 5, following the injection of sodium chloride, excreted in 24 hours 420 cc. of urine with a chloride concentration of 30 m.eq. per liter; following the intravenous administration of 2 cc. of mercupurin, the 24-hour excretion was 3560 cc. of urine with a chloride concentration of 109 m.eq. per liter. For Case 7, whose urea clearance was 37% of normal, the intravenous injection of 24 gm. of salt occasioned the excretion of 1433 cc. of urine with a chloride concentration of 14 m.eq. per liter. Two weeks later, after intravenous administration of 5 cc. of salyrgan the 24-hour output was 3439 cc. of urine with a chloride content of 96 m.eq. per liter. This did not occur in the cases of a control subject (Case 1) and the patient with mild heart failure (Case 3) (Fig. 1).

* The amount of serum cleared of chloride by the kidneys was calculated by the formula: $\frac{U}{B} \times V_c$, when U and B are the urine and serum concentrations of chloride respectively, and V_c is the urine flow per minute, corrected for size on the basis of height.^{3,4}

Discussion. The filtration-reabsorption theory of renal physiology offers two mechanisms which might occasion the impaired excretion of sodium chloride observed in our patients with congestive heart failure. First, the volume of glomerular filtrate may have been diminished below normal, the renal tubules consequently reabsorbing a greater proportion of filtered sodium and chloride without actually increasing their rate of reabsorption of these ions. The fact that in Cases 4 and 5, with severe heart failure, the urea clearance remained at its previous normal or high level during the test suggests that glomerular filtration was not depressed after the injection of salt.

The second, more likely explanation for the diminished urinary excretion of sodium chloride is an increased rate of tubular reabsorption of these ions, the result of circulatory changes in the kidney or of hormonal influences upon the renal tubular cells. Thus, increased venous pressure or renal anoxemia may perhaps stimulate the reabsorption of salt by the tubules. Or the increased tubular reabsorption may be effected by an endocrine mechanism, possibly involving the adrenal cortex,³ set in motion by heart disease or by therapeutic measures instituted during the treatment of heart disease. An abnormally low rate of excretion of ingested sodium chloride has also been observed in patients with diabetes insipidus.¹²

Our data do not indicate whether the observed abnormality involved primarily the excretion of *both* the sodium and the chloride ion, or merely one of the pair. The greater facility with which chloride can be measured explains why the majority of our information is on that ion rather than sodium.

If the retention of ingested salt observed clinically in patients with heart failure is to be explained as primarily due to failure of the kidney to excrete sodium and chloride in normal amounts, an explanation must also be offered for the fact that the concentrations of these ions in the serum of patients with congestive heart failure are not found elevated. Water must be secondarily retained by the kidney, in sufficient quantities to adjust the concentrations of sodium and chloride to the normal range. Instead of salt being excreted in a normal manner, salt, and therefore water are retained; this mechanism was certainly active in our patients with congestive heart failure during the days following an injection of salt, as indicated by the fall in serum electrolyte levels, the increase in weight, and the fall in urine volume.

Summary. 1. In 4 patients convalescent from severe congestive heart failure there was found an impairment of the ability of the kidney to excrete sodium and chloride, (as compared to 2 subjects without heart disease), when the concentration of these ions in the serum was experimentally elevated above normal.

2. Mercurial diuretics increased the excretion of sodium and chloride by these same subjects.

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STUDIES ON "ESSENTIAL" HYPERTENSION.

IV. EARLY ARTERIAL HYPERTENSION.

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STUDIES of patients exhibiting so-called "essential" arterial hypertension have been rewarding in that the coexistence of a variety of abnormalities has suggested that this condition is not a single disease.^{6a} Only those patients have been studied in whom the date of onset of the elevated blood pressure was known. When certain other circumstances occurring at or before the time of onset of the condition were also known, it was sometimes possible to arrive at an opinion regarding the mode of onset, some of the precipitating factors, and the subsequent development of events.

Because facts about the early stages of arterial hypertension appeared important, a group of cases exhibiting slight elevation of blood pressure of short duration were investigated in the hope that some information bearing on the mode of onset of hypertension might be made available. Disturbances of the nervous system and the genito-urinary tract were especially studied in an attempt to ascertain their relation to elevation of the blood pressure.

Material and Methods. Cases were selected when the following conditions were observed: *a*, systolic blood pressure of more than 150 mm. Hg on at least 3 occasions, but which was usually between 140 and 150; *b*, diastolic blood pressure of more than 85 mm. Hg on at least 3 occasions, but which was usually less than 100; and, *c*, the discovery of hypertension on routine examination. Cases in younger subjects were studied, excluding patients with general arteriosclerosis. All cases came because of elevation of the blood pressure, and none because associated disturbances had been discovered.

The usual examinations were always made, some with the view of eliciting

etiologic factors, and others with establishing the existence of the effects of the elevated blood pressure. The former include: a detailed history; physical examination; cursory psychologic examination; studies of the genito-urinary tract, with bacteriologic cultures of the urine, pyelograms after intravenous injection of diodrast, and, when necessary, cystoscopic examination and retrograde pyelography; estimation of the basal metabolic rate; and Roentgen ray photographs of the skull and larger arteries. The latter include: examination of the ocular fundi, physical examination, taking an electrocardiogram and Roentgen ray photographs of the heart, studies of the function of the kidneys (the ability of the kidneys to concentrate urine and the clearance of urea), and measurements of the blood pressure under various conditions.

There were 50 cases in this group; 36 males, 14 females. Thirty-five were under 30 years of age at the onset of the disease, and 15 were under 20. All exhibited elevation of the systolic pressure. The diastolic pressure in all but 9 was on occasions 90 mm. Hg or more. Cases were classified according to the plan proposed by Schroeder and Steele.^{6a} Thirty-seven exhibited lesions of the kidneys, of varying degrees of severity, and were therefore thought to be suffering from "renal" hypertension. In 13 there was no obvious disease of the genito-urinary tract.

Renal function was normal in every case. Basal metabolic rates were not altered. In no instance was the shadow of the heart in Roentgen ray photographs enlarged. Electrocardiograms in a few cases exhibited abnormalities of slight degree. The ocular fundi were essentially normal. Measurements of the blood pressure were significant in that 25 at times exhibited pulse pressures increased out of proportion to the elevation of systolic pressure; diastolic pressures were accordingly often low.

"Renal" Hypertension. Of 37 cases exhibiting lesions of the urinary organs, ureteral obstruction was present in 23, obstruction with infection in 4, infection in 7, and congenital abnormalities in 3 (Table 1). The relation of infection in the urine to the onset of hypertension was fairly well demonstrated in 1 (Case 14). Operative removal of an obstruction at the uretero-pelvic junction in 1 instance resulted in a fall of the blood pressure to normal, although the effect was, of course, slight (Case 10). That mild hypertension occurred as a result of infection (Case 12) and of urinary obstruction (Case 1) was often clear. Only 4 have subsequently developed persistent hypertension. Similar findings at the onset of the disease in other patients exhibiting severe arterial hypertension offer evidence that these individuals are "potentially" hypertensive, and may become permanently so later on.

"Nervous" Hypertension. Thirteen patients exhibited elevation of the blood pressure without organic renal disease. Eleven suffered from psychologic disturbances (Table 2). In 5 psychoneuroses were of sufficient severity to interfere with normal existence (Cases 44 and 45); in 2, such disturbances were not evident on routine examination, but signs of the "diencephalic syndrome"⁴ were present.

Environmental influences were contributory in 7 cases. Ten complained of headache. One had been treated for a benign tumor of the brain, and 1 suffered from neurosyphilis.

An attempt was made to examine separately some of the clinical phenomena which have been considered to be concerned with the existence of hypertension. Because there are often abnormal family histories, various disturbances of the kidneys and the nervous system, and abnormal reactions to environmental influences, these were made the basis of analysis.

The Various Factors Associated With Hypertension. Two factors at least are probably necessary for the occurrence of arterial hypertension: 1, a *constitutional* one, includes a familial tendency to the disease and the patient's general physical and psychologic characteristics, especially those of his nervous system; 2, a *morphologic* one, applies to the existence of renal disease, or renal arteriosclerosis, or the development of nervous tension resulting from environmental influences (in most cases there was evidence of both); 3, a *precipitating* factor, is sometimes exactly known.

Constitutional Component. There existed in 34 of 41 cases a history of arterial hypertension in a member of the family one or two generations before that of the patient, and in 5 others in a member of the same generation. In 7 there was hypertension in the families of both parents. In addition the temperament of almost every patient could be characterized either by the expression, "high strung" or "unstable" to some degree, although the derangement was often well controlled. The diencephalic syndrome was prominent in half. Although in many cases environmental influences were unfavorable, the resultant mental conflict was usually excessive. The level of intelligence of the younger individuals appeared to be above the average; but their reactions to emotional stimuli were often extreme. Emotional instability of some degree occurred in 44 of the 50 patients. Flushing with excitement was common. Most complained of excessive perspiration, and their extremities were usually cold. Many were given to worrying, and became irritable when their affairs were not progressing favorably. These symptoms, it seemed, usually antedated the onset of hypertension, sometimes becoming more prominent as the blood pressure rose.

Morphologic Component. In a majority of patients (37) renal disease of various sorts was found to exist in combination with elements of the constitutional factor (Table 1): Often it also occurred with dysfunction of the nervous system (Case 31), but occasionally alone (Case 24). Relatively severe renal disease as estimated anatomically was associated with very little nervous instability (Cases 1, 12, 14); similarly, slight renal disease with more pronounced nervous disturbance have been found together (Case 26). There was no relation, therefore, between the severity of renal affections and the height of the blood pressure.

Case No.	Name.	Sex.	Age at onset and duration of hypertension (yrs.)	Extremes of blood pressure.		Constitutional components.			Morphologic component.	Albumin in urine. §	Onset with.
				Highest (mm. Hg.).	Lowest (mm. Hg.).	Family history.*	Emotional instability. †	Physical signs. ‡			
1	H. K.	M	16	160/110	124/78	M	++	+++	Horseshoe kidney ?	0	
2	A. L.	M	17	160/90	134/70	S	+++	+++	Sl. rt. hydronephrosis	0	
3	E. B.	M	16	180/80	136/60	M	++	++	Bilat. hydronephrosis	0	
4	B. B.	M	20	180/104	142/88	S	0	+	Sl. bilateral hydronephrosis	0	
5	P. L.	M	22	156/92	132/78	M+	+++	+++	Sl. rt. hydronephrosis	0	
6	C. H.	M	18	150/70	132/86	S	+++	+++	Bilat. hydronephrosis	0	
7	F. G.	M	12	180/100	144/68	M+	+	++	Rt. hydronephrosis	0	
8	P. H.	M	19	162/90	126/54	0	++	++	Double ureters and pelvis	0	
9	G. H.	M	17	150/90	132/74	M	+++	++	Rt. renal ptosis	±	
10	J. P.	M	17	162/68	144/92	M	+++	++	Marked rt. hydronephrosis	0	
11	H. B.	M	22	180/98	144/85	—	+	+++	Blunting of renal calyces	0	
12	L. W.	M	14	182/110	136/60	F M	+	+++	Bilat. hydronephrosis ?	+	
13	J. H.	M	21	160/90	140/82	S	+++	+++	Right hydronephrosis	±	
14	H. M.	M	16	170/94	122/50	F H	+	+++	Right pyelonephritis ?	±	Infection.
15	B. S.	M	16	166/70	134/90	S	+++	++	Dilatation of ureters	+	Infection.
16	C. J.	M	25	162/92	150/70	F	+++	+	Absent left kidney ?	0	Psychoneurosis.
17	C. W.	M	22	180/83	138/80	(F)	++	0	Dilatation of ureter, infection	0	
18	J. J.	M	25	164/100	132/70	M	++	++	Right hydronephrosis	0	
19	P. Z.	M	29	150/90	122/60	?	+++	++	Sl. left hydronephrosis	0	
20	M. S.	M	33	158/110	130/90	M	+++	++	Sl. right hydronephrosis	0	Anxiety.
21	F. R.	M	28	164/94	135/80	M+ F+	++	+	Pyelonephritis, old	±	
22	H. M.	M	29	160/100	138/80	M+ F+	0	+	Sl. right hydronephrosis	0	
23	M. M.	M	34	170/90	132/70	F (M)++	0	+	Pyuria ? infection	0	
24	M. W.	M	32	170/110	134/90	M	+	0	Bilateral hydronephrosis	±	
25	P. F.	M	36	150/90	126/80	M	0	+	Pyuria	0	
26	D. R.	F	30	174/106	140/82	M	+++	++	Angulation of ureters	0	Worry over disease.
27	S. S.	F	34	164/110	122/88	M+	++	+++	Sl. right hydronephrosis	0	
28	J. H.	F	50	178/100	140/80	M	+	+++	Angulation, right ureter	0	Husband's death.
29	P. M.	F	47	184/94	140/70	M	++	+++	Rt. ptosis and hydronephrosis	0	Economic worry.
30	R. M.	F	53	184/116	134/90	M	+++	+++	Right ptosis and hydronephrosis, infection	+	Infection?
31	G. W.	F	36	162/100	142/80	M	+++	++	Rt. kid., poor func., hydronephrosis	+	Preg. and emot. crisis.
32	G. F.	F	23	182/110	124/74	F+	++	++	Bilat. "embryonic" kidneys	±	
33	V. T.	F	40	150/90	128/84	—	+++	+++	Sl. bilateral hydronephrosis	0	Worry, child ill.
34	L. H.	M	25	160/90	128/70	(M)	++	+	Left hydronephrosis	0	
35	V. W.	M	17	160/88	128/64	?	+++	+++	Infection ?	0	
36	L. B.	M	48	156/116	126/92	M	++	0	Calculus and infection	+	
37	M. O. B.	F	20	182/100	132/60	F (M)+	+++	+	Sl. right hydronephrosis, obesity, irregular menses	+	

TABLE 2.—MILD ARTERIAL HYPERTENSION WITHOUT RENAL DISEASE.

Case No.	Name.	Sex.	Age at onset and duration of hypertension (yrs.).	Extremes of blood pressure.		Constitutional components.			Morphologic component.	Albumin in urine. [§]	Onset with:
				Highest (mm. Hg.).	Lowest (mm. Hg.).	Family history.*	Emotional instability.†	Physical signs.‡			
38	S. K.	F	22	158/86	121/70	(M)++	+++	+++	Emotional tension	0	Marriage.
39	B. P.	F	19	148/92	122/80	F	++	++	Emotional tension, worry	=	Brother's death (hypertension).
40	L. S.	F	41	160/100	140/82	(M)+	+++	+++	Psychoneurosis, anxiety	0	Economic reverses.
41	S. D.	F	28	168/100	112/80	(M)+++	+++	+++	Psychoneurosis, anxiety	0	Pregnancy.
42	H. F.	M	20	170/100	110/82	M+(F)++	++	++	Not found	0	
43	J. F.	M	42	180/110	135/88	?	+++	++	Neurosyphilis? psychoneurosis	=	
44	C. R.	M	28	190/115	125/95	(F)	+++	0	Hysteria; anxiety state	0	Marital maladjustment.
45	H. R.	M	27	190/110	140/90	0	+++	+++	Psychoneurosis?	0	Marital maladjustment.
46	F. B.	M	17	160/90	120/70	?	+++	+++	Emotional tension	0	Adverse home environ.
47	J. E.	M	17	162/110	118/70	?	+++	+++	Not found	0	
48	S. F.	M	23	180/100	141/88	F	+++	+++	Emotional tension, worry	0	Econ. maladjustment.
49	H. M.	M	28	180/110	131/86	—	+++	++	Psychoneurosis	0	
50	H. R.	F	41	186/114	146/90	M	+++	+++	Anxiety state; brain tumor	=	Econ. maladjustment.

* Family history: M = mother is hypertensive.

F = father is hypertensive.

(M) = hypertension present in family of mother.

(F) = hypertension present in family of father.

+ = preceded by M or F = each member of mother's or father's family with hypertension.

S = hypertension present in a sibling.

0 = none; — = unknown; ? = possible but uncertain.

† Emotional instability—graded + to +++.

‡ Physical signs—"Diencephalic" blush, excessive perspiration, cold extremities, dermatographia are each represented by +

§ Albumin in urine—by heat and acetic acid test: = = slightest possible trace, approx. 0.7 to 0.14 gm., protein per L.;

+ = faint trace, approx. 0.15 to 0.3 gm., protein per L.

In 11 of the remaining 13 cases nervous dysfunction had developed without renal disease (Table 2). Psychoneuroses were present in 6 cases; emotional disturbances in 5. These existed in combination with elements of the constitutional factor. In 1 instance hypertension appeared to have been influenced by treatment of an anxiety state (Case 44).

Precipitating Factor. In 5 instances emotional crises coincided with the onset of hypertension (Case 31). In 2 the onset occurred during pregnancy. In 2 infection of the urinary tract was present as a precipitating event (Case 14). In the remainder either the exact date of onset was not known, or gradually increasing emotional tension developed from adverse environmental influences. It could usually be inferred that the causes of such adversities lay in the individuals and not in their environments.

Case Reports. CASE 1.—H. K., a 19-year-old student, first became aware of arterial hypertension when he was 16, his blood pressure having been normal at age 15. At 17 he complained of headache, dizziness, and slight nausea. His mother developed hypertension at 40, and his sister also exhibited slightly elevated blood pressure. He blushed markedly all his life, perspired excessively, but denied emotional upsets. He was conscientious about his work, and his grades in college were excellent. On examination a blotchy, well-demarcated blush was seen over his cheeks, back and shoulders. His hands and feet were cold, slightly swollen, and intensely cyanotic, with a purple color slowly fading to dead white after elevation for a few minutes. His urine was not abnormal, and the function of his kidneys was not disturbed. Pyelograms taken after intravenous injection showed bilateral hydronephrosis, more marked on the right side. From the appearance of the films the presence of a horseshoe kidney was suspected. There was no infection. The blood pressure varied between 160 and 128 mm. Hg systolic and between 110 and 78 diastolic during 3 years of observation.

Summary (Case 1). Bilateral ureteral obstruction accompanied slight arterial hypertension in a young man with acrocyanosis and some of the components of the blushing syndrome.

CASE 10.—J. P. was 17 years old when slight hypertension was discovered on routine examination. His mother's systolic blood pressure was 184 and her diastolic 122 mm. Hg; 1 of her sisters suffers from a diseased kidney. At 17 his systolic blood pressure was over 140 mm. Hg, but on a subsequent examination it was normal. He was accepted as a recruit in the Navy. His mother refused to allow him to enlist because of his age, but the next year he applied for the Marines. His systolic pressure was found to be 160.

Physical examination disclosed nothing remarkable. There was marked dermatographia, his extremities were cold and moist, and a diffuse blush appeared on his face and chest after excitement. He was a tense, overactive, excitable, unstable individual, angering easily, becoming easily aroused, and relaxing with difficulty. There were no albumin or white blood cells in his urine, and on culture no organisms were grown. Pyelograms made after intravenous injection showed slight dilatation of the left renal pelvis. Angulation of the ureter was detected at the uretero-pelvic junction; on the right side there was an obvious abnormality which on retrograde

pyelography was found to be marked hydronephrosis with obstruction at the uretero-pelvic junction. In 30 minutes the right kidney excreted 13% of phenol red injected intravenously, the left 21%. His blood pressure varied from 164 to 144 mm. systolic and 94 to 60 mm. Hg diastolic. His two kidneys were able to concentrate urine to a specific gravity of only 1.016, but the clearance of urea was normal. Plastic repair (nephropexy) of the right kidney was performed by Dr. G. W. Fish in March, 1939; a large aberrant artery was found crossing the uretero-pelvic junction causing the constriction. Two months later his blood pressure was within normal limits, his kidneys were able to concentrate urine to a specific gravity of 1.025, and pyelograms showed that there was less obstruction on the right side. Six months after operation his blood pressure was normal, where it has remained, and he was accepted for enlistment in the Army.

Summary (Case 10). Arterial hypertension developed in a young man with marked hydronephrosis, and an unstable psychologic disposition. There was hypertension in the family. Relief of the obstruction by operation resulted in a return of the blood pressure to normal. The subsequent course is naturally in doubt.

CASE 12.—L. W. was an 18-year-old student. Both his father and mother suffer from arterial hypertension, the former also of some disease of his kidneys. Aside from otitis media at 3 his past was unimportant. He had always blushed with excitement, but denied emotional instability. He perspired excessively. His blood pressure was first found elevated on routine examination at the age of 14. He had complained of mild but frequent headaches and difficulty in concentration on his studies since the age of 17.

There was little of importance to be made out on physical examination. He was moderately obese. The function of his kidneys was normal. His heart was not enlarged in Roentgen ray photographs, and there were no abnormalities in the electrocardiogram. There was minimal albuminuria, but in the sediment were white blood cells, singly and in clumps. Cultures of the urine showed many colonies of streptococcus, Group D (Lancefield). Pyelograms taken after intravenous injection demonstrated slight but definite dilatation of ureters and renal pelves, and the calyces were somewhat blunted. His systolic pressure varied from 170 to 135 mm. Hg and his diastolic from 98 to 60 during 2 months' daily observation. He was given calcium mandelate by mouth for 2 weeks, and the number of organisms in each cubic centimeter of urine gradually decreased until the urine became sterile. One month later the same organisms were again obtained in cultures of the urine, again disappearing after the administration of calcium mandelate. This sequence of events had continued. Therapy had no effect upon the level of his blood pressure which remained slightly elevated.

Summary (Case 12). Arterial hypertension of mild degree lasted 4 years. The urine was infected, and lesions were observed in both kidneys. Treatment of the urinary infection did not affect the blood pressure.

CASE 14.—H. M. was a 17-year-old student. His father died of hypertension and uremia associated with one markedly contracted kidney; his paternal grandmother and 2 paternal uncles exhibit it. His appendix had been removed at the age of 15. Because of his family history, he had been observed since the age of 12, at which time his systolic pressure was 106 and his diastolic 54 mm. Hg. "Cold pressor test" gave a normal response, his systolic pressure rising 12 mm. Hg and his diastolic 6. At 13 his systolic

pressure was 130 and his diastolic 70; at 14, 122 and 78; at 15, 136 and 60 mm. Hg. When he was 16 he complained of lack of energy, fatigue, and slight dysuria, and he noticed emotional instability and irritability. Because his systolic pressure was 160 and his diastolic 80 mm. Hg he was studied in the hospital.

Aside from the presence of cold, moist extremities and dermatographia physical examination showed nothing remarkable. There was no albumin in the urine but microscopic examination disclosed the presence of many white blood cells singly and in clumps. Culture of the urine showed innumerable colonies of non-hemolytic streptococcus Group D (Lancefield). Pyelograms made after intravenous injection of diodrast demonstrated slight dilatation of the upper two-thirds of the right ureter, and blunting of the upper calyx of the right kidney; these findings were confirmed by retrograde pyelography which failed to disclose a cause for the dilatation. White blood counts and erythrocyte sedimentation rates were within normal limits, and there was no fever.

For a month in the hospital his systolic pressure varied from 170 to 118 and his diastolic from 94 to 50 mm. Hg. Therapy with sulfanilamide, urotropin, and calcium mandelate failed to eradicate the infection, but resulted in lowering the number of colonies of bacteria in the urine to 14 per cubic centimeter. When therapy was stopped, the number of colonies increased markedly. During the following year his blood pressure fell to normal levels when the infection was partially controlled, rising when the bacterial count in his urine was high. One year later he suffered two attacks of pyuria, with pain, nausea, and dysuria; his blood pressure again became further elevated during the acute episode. The same organism was found in his urine. The right ureter was therefore dilated by Dr. John Robinson in March, 1940; since then he has remained free of infection and his blood pressure has been normal.

The patient was a rather tense, shy individual, emotionally unstable but extremely active in school. He was well liked by his classmates, and attained a position of importance in the direction of their activities. He had always blushed easily when emotionally aroused, worried too much about his responsibilities and often became depressed. He perspired excessively, and his hands and feet were continually cold and moist. His tendon reflexes were hyperactive.

Summary (CASE 14). Arterial hypertension of slight degree became manifest coincidentally with infection of the urinary tract in a boy of 16, and was eventually controlled by relief of ureteral obstruction. There was hypertension in his family. He demonstrated signs of emotional and autonomic instability.

CASE 24.—M. W. was a 42-year-old physician, who first exhibited elevated blood pressure at the age of 32. His mother and one sister have slight hypertension. Between the ages of 23 and 38 he suffered 6 attacks of renal colic; 2 small calculi were passed. His blood pressure varied from 170 to 144 mm. Hg systolic and 110 to 92 diastolic during 4 years' observation. He was an overconscientious and serious-minded individual, but did not worry to excess in spite of having many reasons for so doing. He did not consider himself emotionally unstable, and controlled himself well.

Important findings on examination were confined to the kidneys. There was bilateral hydronephrosis, greater on the right, and a small calculus was seen in the lower calyx of each kidney. There was obstruction at the right uretero-pelvic junction. There was no flush to be seen, and perspiration was not excessive. No essential change in his condition has occurred.

Summary (Case 24). Arterial hypertension was associated with relatively severe anatomic changes in the kidneys in a man with very little nervous instability.

CASE 26.—D. R. was 30 years old when her blood pressure was first elevated. Her mother died of hypertension and apoplexy. At the age of 26 she was told that she was suffering from a venereal disease, and she was treated weekly by injection for 2 years. This fact caused her great worry, and she began to brood. Her blood pressure was said to have been normal at age 28, but at 30 her systolic pressure varied from 174 to 144 and her diastolic from 106 to 84 mm. Hg. She admitted continuous worry, severe emotional instability, frequent crying spells, and nervousness.

On examination there was a well-marked blotchy blush on the face, neck and chest during excitement. The finger nails were bitten. Marked dermatographia was seen and perspiration was excessive. There were no other abnormalities. The urine was normal, as was the function of the kidneys. The heart was not enlarged in Roentgen ray photographs, and the electrocardiogram was not remarkable. Pycelograms after intravenous injection showed that there was constriction of both uretero-pelvic junctions, the insertion of the ureters being in the upper half of the renal pelves. The right kidney was ptosed. Her systolic pressure varied from 164 to 140 and her diastolic from 100 to 84 mm. Hg during 4 years. No evidence of syphilis was found by examination of the blood and spinal fluid.

Summary (Case 26). Labile arterial hypertension accompanied the hypertensive diencephalic syndrome and slight abnormality of the kidneys. There was in addition prolonged emotional tension.

CASE 31.—G. W. was an emotionally unstable, worrying woman of 37. Her mother suffered from arterial hypertension. She had always blushed easily, perspired excessively, and complained of coldness of the extremities. She had also noticed spontaneous bruises on her legs. Her first pregnancy occurred at the age of 35; a normal infant was delivered. Her second pregnancy occurred the following year; her blood pressure and urine were normal until the first week of the seventh month. At this time her child was seized by convulsions, later discovered to have been associated with teething. She became greatly excited and disturbed but remained calm to all outward appearances. During the next 2 days she felt tired and elated. Her ankles then became swollen, and her physician found marked albuminuria and arterial hypertension. Because of increasing signs of toxemia of pregnancy labor was induced in the middle of the seventh month, and twins were delivered. Her blood pressure remained slightly elevated after delivery.

On examination 3 and 6 months later, there was a vivid but diffuse blush seen on the face and neck during excitement, and the extremities were cold and moist. The lower pole of the right kidney was palpable. The clearance of urea was 103% of normal and the kidneys were able to concentrate urine to a specific gravity of 1.039. There was a moderate amount of albumin in the urine, but no formed elements were found in the sediment, and cultures were sterile. The heart was not enlarged in Roentgen ray photographs. Basal metabolic rate was -14% of normal. Pycelograms after intravenous injection showed that very little diodrast was excreted by the left kidney and that the pelvis of the right was distorted; retrograde pyelography disclosed the presence of right hydronephrosis; there was distortion of the calyces on the left side. In 30 minutes the right kidney was able to excrete 8.6% of the phenol red injected intravenously, and the clearance of urea in this period was 50% of normal; phenol red excreted by the left kid-

ney was 4.1% and the clearance of urea was 35%. Her blood pressure varied from 162 to 142 mm. Hg systolic and 100 to 80 diastolic. It was slightly higher during the following 2 years.

Summary (Case 31). Arterial hypertension became manifest coincidentally with a severe emotional shock sustained during pregnancy. "Toxemia" resulted. Right hydronephrosis and diminished function of the left kidney were found 3 and 6 months later. The presence of infection was not established.

CASE 44.—C. R. was a 28-year-old clerk. Although his paternal grandfather died of apoplexy, there was no definite history of hypertension in his family. His blood pressure was said to have been normal until the age of 28, when his systolic pressure was 140 mm. Hg and his diastolic 90; 1 month later it had risen to 170 systolic and 100 diastolic, and 6 months later to 190 and 115. He did not complain of symptoms.

On examination there was nothing of importance to be made out. Renal function was normal and there were no abnormalities in the urine. The heart was not enlarged in Roentgen ray photographs; the basal metabolic rate was -9% of normal. He appeared to be a quiet, well-controlled, rather stolid and unemotional individual, denying all nervous manifestations. One week after discharge from the hospital he exhibited a typical attack of hysteria associated with an uncontrollable tic of his shoulders and arms which he admitted had been present before. Three months later he was found to be in a state of extreme nervousness, complaining of severe frontal headache and 6 months later these symptoms were unimproved. His systolic pressure varied from 190 to 150 mm. Hg and his diastolic from 120 to 88. He was sent to a psychiatric clinic for investigation; there he was considered to be suffering from psychoneurosis (anxiety state). Treatment was instituted, and subsequently his systolic pressure returned to normal levels, although his diastolic remained between 100 and 85 mm. Hg for 3 years.

Summary (Case 44). Arterial hypertension was associated with psychoneurosis, improving after psychotherapy.

CASE 45.—H. R. was a 30-year-old designer. His blood pressure first became elevated at the age of 27. His maternal grandmother died of hypertension. Except for otitis media and pneumonia his past history was uneventful. He had always been emotionally unstable, but usually remained outwardly calm during periods of intense internal excitement. Perspiration was profuse. He had suffered from frequent occipital headaches for many years, usually brought on by excitement.

Little of importance was made out on examination. A faint blotchy blush was seen over the face and chest, and the extremities were cool and moist. Renal function was normal, and there were no abnormalities in the urine. Basal metabolic rate was -5%. The heart was not enlarged in Roentgen ray photographs, and his electrocardiogram was not unusual. Pyelograms after intravenous injection disclosed normal pelves and ureters. No bacteria were found on culture of the urine. His systolic pressure was variable, with a range of 190 to 140 mm. Hg; his diastolic varied likewise from 120 to 90.

During 2 years' observation it became obvious that he was extremely high strung and nervous. Sometimes he acted in an erratic fashion, and there were many marital and environmental adjustments which he could

not make. He worked at several different trades, did well in all, but refused to remain at a job long enough to secure financial stability for his family. He finally left his wife, and went to another part of the country.

Summary (Case 45). Arterial hypertension was associated with emotional instability in a maladjusted young man of some ability.

Discussion. The cases reported probably represent instances of the earliest stage of arterial hypertension. Every one exhibited at some time elevation of both systolic and diastolic pressures to a degree greater than the limits set by Hines.³ His and other studies^{1,5} indicate that similar individuals often develop persistent arterial hypertension later in life. That renal disease was present in so many of them (74%) is further evidence of the part the kidneys play in arterial hypertension. Diseases of the kidneys occurred too commonly to be explained as coincidences; it is likely therefore that they are concerned with at least part of the cause of elevation of the blood pressure.^{6b} The absence of renal diseases in the remainder suggests that they were present but not demonstrable, or that arterial hypertension is the result of more than one condition. The latter explanation is more likely.

From these and other studies it is possible to draw several tentative conclusions. It is obvious that arterial hypertension is not a single condition resulting from a single cause, but is the result of several factors, one or more of which is dominant. There is little doubt, for example, that organic renal disease and hypertension are intimately associated. That fact emerges when the state of the kidneys is examined;^{6b} but renal disease often exists when the blood pressure is normal. Contrariwise, arterial hypertension may occur without renal disease. Other factors need furthermore to be taken into account, such as the hereditary nature of hypertension² and the tendency to "nervousness" in hypertensive individuals, for many years considered important.

An attempt has been made here to separate those aspects that can be studied from those that cannot. The view taken is that one or more abnormal states is by chance found to affect individuals constitutionally predisposed. Most of the signs of this predisposition can be referred to the nervous system. When an individual exhibits these signs, and subsequently develops renal disease, abnormal emotional reactions to his environment, or one of several other conditions, he becomes subject to hypertension. This conception does not help to explain the precise mechanism, but it does propose a direction for making explorations. The fundamental defect, that of individual susceptibility—the "constitutional component"—remains "essential," or unknown (agnogenic).

In the light of this study it is possible to ascertain some of the effects of hypertension usually regarded as being present in the more advanced stages of the disease as its necessary accompaniments.

For example, elevation of the blood pressure itself either contributes to the usual state of "nervousness" often seen in hypertensive individuals, or nervousness is antecedent to that elevation. In the experience now reported increased nervous tension was known to be present in most of the patients before hypertension was discovered, and was associated with very little elevation of blood pressure after its discovery. This observation suggests that "nervousness" is concerned in the cause of hypertension.

This study has been illuminating in that it has been possible to observe in a group of individuals believed to represent the early stages of a chronic disease, arterial hypertension, certain pathologic and functional derangements with which later stages are associated. These derangements may therefore play a part in causation.

Summary. Fifty patients exhibiting slight elevation of the blood pressure were studied with a view to ascertaining the varieties of clinical disturbance. Thirty-seven were found to be suffering from various diseases of the kidneys, and 11 others from dysfunctions of the nervous system. In addition, every patient exhibited nervous tension of some degree. In a few cases the onset of hypertension was associated with a definite physical or psychologic disturbance. It is probable in the light of this experience that arterial hypertension is the result of a number of factors, differing in different individuals.

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EXPERIMENTAL CHRONIC HYPERTENSION IN THE RAT.*

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Our generally accepted notions concerning the etiology and nature of chronic hypertension are based for the most part on experiments performed on the dog and on clinical observations on human patients. With the development of a relatively simple and

* Aided by grants from John and Mary R. Markle Foundation and from Mr. Joe Werthan.

accurate method for the determination of the blood pressure of the rat (*Mus norvegicus*), it is possible to utilize the advantages which the use of this species offers to investigate many problems not easily solved when the larger mammals or the human are the subjects of study. A variety of procedures lead to the development of chronic hypertension in the rat and may be used conveniently in the investigation of various problems of experimental hypertension.

The Determination of the Systolic Blood Pressure. Systolic blood pressures were determined on unanesthetized adult rats by the method previously described.⁸

This procedure has proved accurate and reliable in our hands. Several precautions, however, may be emphasized which must be taken into account to avoid errors. The rubber sleeve in the plethysmograph must be neither too taut nor loose; otherwise the water manometer will not respond to alterations of bloodflow in the tail. By avoidance of undue tension or slack in the rubber, maximum sensitivity is obtained and only minimal warming of the animal is necessary to give a good reading. Overheating of the animals is to be avoided.

The same criteria are to be applied to the reading of the movement of water in the manometer connected to the plethysmograph as are used in graphic methods for determining the blood pressure in man. The response of the plethysmograph must be sharp and the movement of the column of water should continue when the mercury column is maintained at a point 5 to 10 mm. below the level at which the water column begins to move.

If these precautions be observed and if overheating of the animals be avoided, accurate values are readily obtained and there is little chance of deception by too low values due to inadequate dilatation of the arteries in the tail or too high values induced by overheating.

Effects of Various Procedures on Blood Pressure. Most of the rats used were of a piebald strain reared in the laboratory. Some of a pure-bred Wistar strain were obtained from a commercial breeder.

Hypertension has been induced by the following methods: 1, by the procedure of partial nephrectomy; 2, by the application of silk to the renal cortex; 3, by the application of a collodion capsule to the kidney; 4, by the injection of a suspension of kaolin into the cisterna magna; 5, by the administration of excessive doses of certain steroidal compounds; and 6, by the administration of various nephrotoxic agents. In addition to the increased blood pressure following the above procedures, hypertension has been observed to occur in certain other rats. In some of these the presence of spontaneous hydronephrosis probably accounts for the existing hypertension. Other animals had been subjected to various experimental diets and these observations will be described in a later communication.

1. *Partial Nephrectomy.* The procedure of partial nephrectomy consists in ligating the poles of one kidney and removing the other, as described by Chanutin and Ferris.¹ This procedure suffers from the defect that it requires accurate estimation of the amount of renal tissue to be removed. If too much be extirpated, the animal succumbs within a few weeks, due to the development of renal insufficiency or malignant hypertension or both. On the other hand, if too little tissue be removed, no appreciable elevation of the blood pressure results.

The renal stump remaining after partial nephrectomy is frequently closely adherent to the surrounding viscera (liver, spleen) and large blood-vessels may be seen to be growing into the renal substance from its adherent tissues. This is particularly apt to occur if one amputates the poles of the kidney by cutting rather than by ligation, as recommended by Chanutin and Ferris. To avoid the formation of this collateral blood supply which may prevent the development of hypertension we have adopted the procedure of cauterizing the cut surface of the kidney.

Although used exclusively for our earlier studies, the method of partial nephrectomy has proved much less satisfactory than the application of silk to be described next. Attempts to induce hypertension by scarring the surface of the kidney, by the cautery, or by the application of escharotics (silver nitrate, tincture of iodine, phenol) proved futile. Mere destruction of the renal cortex is unsatisfactory, since it either fails to induce hypertension or results in so much renal destruction as to induce a rapidly fatal renal insufficiency.

2. *The Application of Silk.* For the induction of chronic hypertension experimentally we have found the application of silk to be the procedure of choice. This method was first described for the dog by Page.⁶ In applying it to the rat, the following method is used.

A piece of silk* (the cloth commercially designated as "crepe" silk is best) is cut into oval shape. Four V-shaped pieces are cut out at each quadrant and a purse-string suture is passed around the edges (Fig. 1). The kidney is exteriorized through a lumbar incision, the capsule broken and pushed aside by gentle pressure with a gauze sponge and the silk applied (Fig. 1). The suture is drawn together and tied. Care must be taken to avoid obstruction of the ureter or renal pedicle. It is only necessary to apply the silk lightly. The application of the ligature just below the poles prevents the silk from slipping off when the kidney is replaced in the abdomen.

Except in rare instances where a rat has a spontaneous slightly elevated blood pressure prior to the procedure described above, it is necessary to apply silk to the other kidney in order to obtain permanent elevation of the blood pressure. This is done about 1 week

*. Cotton cloth is equally satisfactory and has been substituted for the silk in all our recent experiments.

following the first operation. Extirpation of the second kidney results, in many animals, in a rapidly developing malignant hypertension and death within a few weeks following nephrectomy. Where the more chronic type of hypertension is desired, the bilateral operation, as just described, is necessary.

The above described procedure has proved satisfactory in our hands. The use of cellophane instead of silk, as originally advocated by Page⁶ in the dog, is rather cumbersome when applied to the rat and in our experience is unsatisfactory, due to the development of a "foreign-body" reaction with erosion of contiguous organs. The immediate mortality of the operation when using silk is low and if care be taken to avoid compression of the pedicle, the animal develops hypertension gradually and remains in good health for some months.

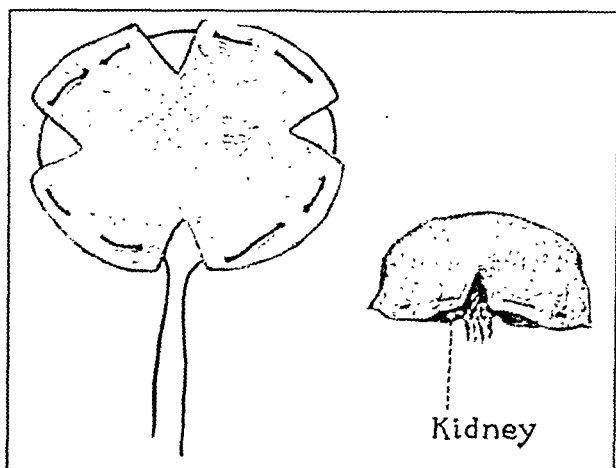


FIG. 1.—Application of silk to the kidney. The drawing on the left illustrates the manner in which the silk is prepared with a purse-string silk suture. On the right is shown the appearance of the kidney with the silk applied. Note that the renal hilus is not compressed by the procedure.

A distinct rise in blood pressure following the application of silk bilaterally may be evident within 10 days following the second operation, but usually does not occur until several weeks have elapsed.

A typical result following the application of silk is illustrated in Chart 1, which depicts the blood pressure curve of a single rat observed for more than 4 months. Except for the irregularity during the third week following the application of silk to the second kidney, the curve shows a uniform and gradual rise until just a few days before the death of the animal, when there is a precipitous pre-mortem drop. By the time the systolic pressure attains a level of 200 mm., there is evidence of renal insufficiency, the animal develops

uremia, becomes anemic, loses weight and manifests a general state of debility in which it succumbs.

The age of the animal is an important factor in determining the reaction of the rat to the application of silk to the kidneys, as well as to the procedures to be described next. Young animals, even after reaching maturity, react poorly and tend to develop uremia and malignant hypertension. Older animals (over 1 year of age) withstand the operations better and tend to develop a chronic form of hypertension.

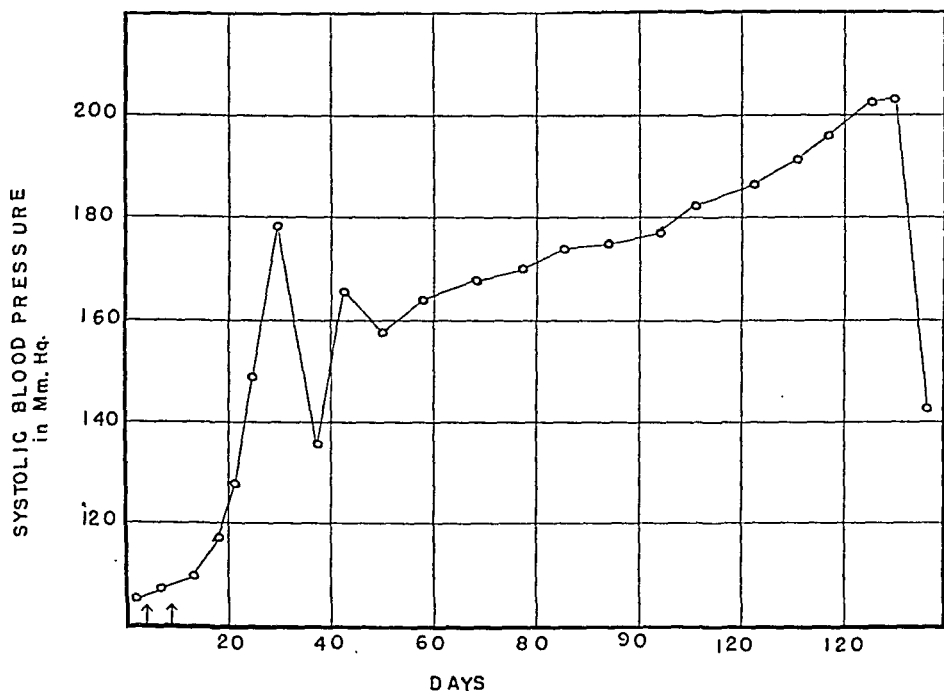


CHART 1.—Variations in the systolic blood pressure of a rat following the application of silk bilaterally. The arrows indicate the application of the silk with an interval of 5 days between the operations on the two kidneys. Note the temporary elevation which occurred about 3 weeks following the operation with the subsequent remission. After 6 weeks the blood pressure curve remains at a hypertensive level, rising gradually over a period of 5 months when it drops precipitously before the death of the animal.

3. *The Application of a Collodion Capsule.* Another satisfactory procedure for inducing hypertension in rats consists in applying a coat of collodion to the renal cortex. This may be done by covering the decapsulated kidney with a single layer of ordinary surgical gauze and applying collodion.* The kidney should remain exteriorized for several minutes until the solvent evaporates from the solution of collodion, leaving a white firm coat on the kidney.

A collodion capsule may also be applied using silk, as described in the preceding section. For this purpose silk of the type used in

* The use of collodion was suggested to us in a conversation with Dr. W. Dock. (See also Page, E. W., Patton, H. S., and Ogden, E.: *Am. J. Obst. and Gynec.*, 41, 53, 1941.)

the manufacture of women's stockings is desirable. The collodion is applied after the silk has been tied over the kidney in the usual manner.

The application of collodion to the kidney results in more extensive injury to the organ than when silk alone is applied. Removal of the second kidney is usually followed by a rapid elevation in blood pressure and death of the animals in a short time. A number of animals develop hypertension following a unilateral operation. In those which fail to develop hypertension in the course of 6 to 10 weeks, the application of silk alone (without collodion) to the other kidney will usually result in hypertension.

4. *Other Procedures.* Partial occlusion of one renal artery with removal of the kidney on the opposite side, as suggested by Rytand,⁷ has not proved entirely satisfactory in our hands. It is difficult to estimate the degree of occlusion in such a way as to avoid the death of the animals from acute renal insufficiency by too tight a ligature or failure of hypertension to develop if the ligature be applied too loosely. The method of Drury,² which was devised for the rabbit, was also unsatisfactory when applied to the rat, leading usually to acute renal insufficiency and death of the animals within a few weeks following the removal of the hypertrophied kidney.

Hypertension has occurred spontaneously only very rarely in our colony of animals. Its incidence in young animals is less than 1%. The production of hypertension by manipulation of the animal's diet will be described in detail in a separate publication.

The hypertension which follows injection of kaolin into the cisterna magna has been described by Griffith and his collaborators.³ The induction of hypertension by steroids has also been previously described.⁴

In view of the variety of substances which are available for producing renal damage, it was thought that some of these might incidentally also induce hypertension. This procedure has, in general, not proved satisfactory in our hands. We have administered a number of agents which induce renal injury (bichloride of mercury, uranium nitrate, cantharides, lead nitrate, various sulfonamide derivatives, and so on) in doses which were fatal to only 10% to 20% of the animals. In only approximately 10% of all animals in which marked renal damage had been produced did a moderate degree of hypertension develop. This result is compatible with the view that renal damage alone does not result in hypertension but that a specific portion of the nephron must be affected before hypertension develops. This point of view will be dealt with more fully in a separate communication.

Discussion. The procedures outlined afford a means of inducing hypertension by what appears superficially to be a variety of unrelated agencies. There would thus appear, offhand, to be little connection between the hypertension resulting from injecting kaolin

into the cisterna, the feeding of sterols, and the application of silk to the kidney. Nevertheless, as discussed elsewhere,⁵ there is evidence which suggests that all of these procedures may act directly or indirectly through the kidney and thus give rise to hypertension of renal origin.

For practical purposes the bilateral application of silk is, in our experience, the optimal method for inducing chronic hypertension. By this procedure, mortality is slight and the resulting hypertension is of long duration. With more intensive procedures, the hypertension resembles that of malignant hypertension, as observed in man, the blood pressure rising to very high levels in a period of several weeks and the animal rapidly succumbing in uremia.

Summary. A variety of procedures are outlined by which it is possible to induce chronic hypertension in the rat. The most practical of these procedures consists in applying silk to the kidneys. This is accompanied by relatively low operative mortality and usually results in a permanent elevation of pressure to hypertensive levels. The blood pressure responses to various other operative procedures on the kidneys are described.

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SERUM CHOLESTEROL AND ATHEROSCLEROSIS IN CHRONIC GLOMERULONEPHRITIS.

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THE observation that atherosclerosis occurs commonly in individuals dying of renal disease is generally accepted. Ophüls^{6a} reported that in a group of 155 autopsies of cases of chronic lesions in

the kidney, 93% had definite and frequently marked atherosclerosis. Likewise, more recent studies by Fishberg⁴ and by Addis and Oliver¹ report a similar incidence. One of the postulated factors as an explanation for the almost constant coexistence of the two processes is the elevation in serum cholesterol which may occur during some stage of the renal disease.^{3,6} In view of the great frequency of atherosclerosis in individuals over the age of 40 years, it was felt desirable to determine first the incidence of atherosclerosis in young persons dying of renal disease and, second, the frequency and the extent of elevation of the serum cholesterol in such patients.

Material. Two groups of patients were studied. In the first, the clinical records and autopsy protocols of 54 patients under the age of 40, who had died of subacute or chronic glomerulonephritis at the Presbyterian and Babies' Hospital during the past 10 years, were examined. The incidence of these two types of renal disease in this group was as follows: chronic glomerulonephritis in 47 instances, subacute glomerulonephritis in 7. The serum cholesterol values were tabulated. The degree and extent of gross aortic and coronary atherosclerosis as noted by the pathologists was recorded and subdivided into three classes: mild, moderate, and marked. Mild atherosclerosis was considered to be present if several small, raised, yellow plaques were visible in either the aorta or coronary arteries. Marked atherosclerosis was designated to include widespread, numerous lesions. Moderate atherosclerosis was considered to fall between these two extremes.

In the second group, the case records of 18 patients with chronic glomerulonephritis who were being closely observed at the Research Service, First Division, Welfare Hospital over periods up to 2 years were examined and the serum cholesterol determinations tabulated. In this study all of the cholesterol determinations were done on serum by the method of Bloor, Pelkan, and Allen² except 8 patients in Group I under the age of 10 years in whom the method of Schoenheimer and Sperry⁷ was used. In the first group, cholesterol determinations had not been done frequently and values were available in only 30 of the 54 cases.

In the second group of patients cholesterol determinations were made at approximately monthly intervals. The number of recorded values in each of the patients varied from 4 to 23, averaging 8 for the group.

Occurrence of Gross Atherosclerosis. An analysis of the pathology protocols of the 54 patients in the first group, individuals age 1 through 39 dying of renal disease, revealed that gross atherosclerosis of the aorta occurred in 52 instances, or in 96% of the group. Coronary atherosclerosis was recorded in 38 instances, or in 70% of the group. Coronary atherosclerosis was not present in the absence of at least mild aortic lesions. Table 1 reveals the incidence and extent of gross aortic and coronary atherosclerosis in the patients of this group who were subclassified according to age into the four decades. It is of interest that gross mild to moderate aortic atherosclerosis was present in 7 of the 8 individuals in the age group 1 to 9 years. No coronary lesions were observed in this group. However, in the next three decades, coronary atherosclerosis was

almost as prevalent as aortic atherosclerosis. The lesions were more widespread and frequently of greater magnitude in the third and fourth decades (see Table 1).

TABLE 1.—OCCURRENCE OF GROSS AORTIC AND CORONARY ATHEROSCLEROSIS IN GROUP I (54 PATIENTS, AGE 1 TO 39, DYING OF CHRONIC GLOMERULONEPHRITIS).

Age groups (in years):	0-9.	10-19.	20-29.	30-39.	Total.	%.
Number of patients	8	7	18	21	54	
Aortic atherosclerosis	7	6	18	21	52	96
Mild	4	3	3	5	16	
Moderate	3	3	12	12	31	
Marked	0	0	3	4	7	
Coronary atherosclerosis	0	5	16	17	38	70
Mild	0	3	7	7	17	
Moderate	0	2	8	8	18	
Marked	0	0	1	2	3	

The prevalence of atherosclerosis of the aorta and coronary artery in this group may be compared with the incidence of lesions in 54 patients in the same age groups selected at random from the autopsy records (Table 2).

TABLE 2.—OCCURRENCE OF GROSS AORTIC AND CORONARY ATHEROSCLEROSIS IN A CONTROL GROUP OF 54 PATIENTS COMPARABLE IN AGE TO GROUP I.

Age groups (in years):	0-9.	10-19.	20-29.	30-39.	Total.	%.
Number of patients	8	7	18	21	54	
Aortic atherosclerosis	0	1	6	12	19	35
Mild	0	1	5	8	14	
Moderate	0	0	1	4	5	
Marked	0	0	0	0	0	
Coronary atherosclerosis	0	1	2	8	11	19
Mild	0	1	2	6	9	
Moderate	0	0	0	2	2	
Marked	0	0	0	0	0	

The only persons excluded from this sampling were those dying of renal disease comparable to Group I. An analysis of the autopsy protocols of the control series revealed that gross aortic atherosclerosis was present in 19 individuals, or in 35% of the group. Gross coronary atherosclerosis was recorded in 11 instances, or in 19% of the 54 patients.

The difference between the two groups is more striking in the first two decades since atherosclerosis was present in 14 out of 15 instances in Group I, in contrast to only 1 of the 15 in the control group. In addition, the degree of lipid infiltration, when present in this group, is less marked than in the Group I patients dying of renal disease (Table 2).

Serum Cholesterol Values in 54 Patients With Glomerulonephritis (Group I). Serum cholesterol determinations were recorded in 30 of the 54 patients in Group I. A total of 77 determinations had been made. In 11 of the individuals, 3 or more determinations were available. In 17 of the 30 patients, the serum cholesterol value

exceeded 300 mg. per 100 cc., in 11 the value exceeded 400 mg. per 100 cc., and in 7 the value exceeded 600 mg. per 100 cc. The following abstract is characteristic of the cases that were followed over long periods of time.

CASE 1.—E. D., a white schoolgirl, aged $11\frac{1}{2}$ years, entered the Babies' Hospital on July 16, 1937, with the history of pallor and generalized edema of $4\frac{1}{2}$ months' duration. In the past history, the patient had had tonsils and adenoids removed at the age of $2\frac{1}{2}$, and scarlet fever at the age of 8 years. Subsequent urine examinations were negative. Onset of the present illness was preceded by an upper respiratory infection, *i. e.*, "stuffy nose" and sore throat. Swelling of eyelids first appeared and then became generalized. Urine examination showed albumin, red blood cells, white blood cells, and casts. Edema gradually became worse in spite of fluid restriction and the patient was admitted to the hospital.

On physical examination, the patient was very pale and had generalized anasarca. She was alert, coöperative, and not uncomfortable. The temperature was 99.8° F., the pulse rate 90, respiratory rate 20, and the blood pressure 160/110. There was a moderate thickening of both mid-turbinate with a mucopurulent discharge. In the fundi the arteries were constricted and the nerve head slightly elevated. The lungs were clear. The heart was normal. In the abdomen, shifting dullness was present. No masses or organs were felt. There was no lymphadenopathy or abnormal neurologic findings.

Laboratory data on admission revealed red blood cells 3,350,000, hemoglobin 11.9 gm. per 100 cc., white blood cells 13,000 with 69% neutrophils. The urine was straw-colored, cloudy, with a specific gravity 1.022, albumin 4+, and the urinary sediment contained red and white cells with granular and hyaline casts. The blood urea nitrogen was 10 mg. per 100 cc., the total serum proteins 3.35 gm. with albumin 1.52 and globulin 2.05 gm. per 100 cc. Six serum cholesterol determinations were recorded. On March 17 the serum cholesterol was 689 mg., on April 3, 717 mg., on April 13, 724 mg., on May 3, 686 mg., on June 2, 611 mg., and on June 28, 280 mg. The patient was placed on a high protein diet, low in salt, with fluids restricted to 1000 cc. daily.

She felt fairly well with edema moderately well controlled by diuretics until June 24, when chills and fever developed with signs of peritonitis. Blood and abdominal fluid culture revealed pneumococcus Type XVIII. The patient gradually failed and died on June 29.

On postmortem examination the following diagnoses were made: 1, Chronic glomerular nephritis; 2, anasarca and ascites; 3, cardiac hypertrophy, mild; 4, septicemia; 5, peritonitis; 6, atheromata of aorta and coronary arteries. The gross lesions in the aorta and coronary arteries were elevated, yellow atheromatous patches. These were present in the anterior descending branch of the left coronary and in the right coronary artery as well as in the aorta. These lesions were especially numerous just above the sinuses of Valsalva.

Serum Cholesterol Values in 18 Patients With Chronic Glomerulonephritis Now Being Observed (Group II). The serum cholesterol values in the 18 patients with chronic glomerulonephritis (Group II) are compiled in Table 3. In each of the individuals, the total number and range of serum cholesterol determinations, together with the number of values above and below 400 mg. per 100 cc. are recorded. In 17 of the 18 individuals the high cholesterol value

exceeded 400 mg. per 100 cc., and in 10 of the 18 the high value exceeded 600 mg. In contrast, the low serum cholesterol value for each patient varied from 167 to 450 mg. per 100 cc. In 9 of the individuals the low value was less than 300 mg.

TABLE 3.—SERUM CHOLESTEROL VALUES IN 18 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS (GROUP II).

Pt.	Age.	Sex.	No. of determina- tions.	No. of determina- tions over 400 mg. per 100 cc.	No. of determina- tions under 400 mg. per 100 cc.	Range of serum chol., mg./100 cc.	
						High.	Low.
A. L.	14	M	5	2	3	446	375
H. B.	24	F	19	10	9	537	292
S. R.	26	F	6	6	0	610	450
J. T.	25	M	6	3	3	1000	317
A. P.	17	F	12	0	12	339	167
E. B.	23	M	10	3	7	610	225
H. R.	25	M	5	3	2	458	384
A. A.	28	F	4	1	3	438	251
C. M.	41	M	4	3	1	450	355
A. H.	51	M	6	4	2	948	274
W. E.	17	M	5	3	2	807	305
P. B.	30	M	5	4	1	617	370
J. W.	21	F	5	2	3	400	300
D. G.	20	M	4	2	2	792	397
H. P.	17	F	23	2	21	417	250
D. L.	26	M	4	1	3	447	255
A. R.	36	M	13	7	6	730	310
E. T.	41	F	12	10	2	710	297
Total	143	77	66		

(Normal values, variously given, range about 140-300 mg. per 100 cc.)

It is evident from Table 3 that if only isolated determinations of serum cholesterol had been made, a number of instances of significant hypercholesterolemia would not have been observed, for in 66 of the 143 determinations the value obtained did not exceed 400 mg. per 100 cc. The period of hypercholesterolemia was associated in most instances with an edematous phase of glomerulonephritis. From clinical observation of these patients over long-term periods it was observed that when the edema subsided, the serum cholesterol values fell towards normal levels.

Discussion. Atherosclerosis has been found to occur in 96% of the individuals (age: 1 through 39 years) dying of renal disease in the group studied, in contrast to 35% in a control group with the same age distribution. This difference between the groups is more striking when compared with the incidence of atherosclerosis obtained by Ophüls^{5b} in a statistical survey of 3000 autopsies. This author reported only a few scattered cases during the first two decades, 3.5% during the third decade, and 9.2% during the fourth decade. The greater incidence of atherosclerosis in the control group as compared to this large series may be explained in part by the interpretation of the presence of atherosclerosis. If several raised, yellow, intimal lesions were present in either the aorta or

the coronary arteries, this was regarded as sufficient for a diagnosis of mild atherosclerosis.

It has also been shown in the above data that hypercholesterolemia almost invariably occurs in patients with chronic glomerulonephritis during some stage of the disease process—particularly in association with the nephrotic stage. Likewise there is considerable fluctuation in the serum cholesterol levels in these patients in contrast to normal individuals in whom the cholesterol level has been found to remain relatively constant over long periods of time.⁸⁻¹⁰ The hypercholesterolemia, which occurs in other diseases, namely myxedema and poorly controlled diabetes, is likewise associated with a high incidence of atherosclerosis. It seems possible, therefore, that the elevation in serum cholesterol which occurs in renal disease is one of the factors responsible for the development of aortic and coronary atherosclerosis.

It has also been demonstrated that atherosclerosis has occurred with great frequency in a young age group, in which atherosclerosis ordinarily is relatively rare. For this reason, the etiologic significance of senescence which is so frequently considered paramount in the development of atherosclerosis can be depreciated, at least as far as the present study is concerned.

Conclusions. 1. Fifty-two of 54 patients (96%), aged from 1 through 39 years, dying of chronic glomerulonephritis, had gross aortic atherosclerosis. In 38 (70%) of these patients, gross coronary atherosclerosis was present.

2. Serum cholesterol values in 30 of these 54 patients exceeded 300 mg. per 100 cc. in 17. In 12 of these individuals the value exceeded 400 mg. per 100 cc.

3. Serum cholesterol studies have also been carried out in a group of 18 patients with chronic glomerulonephritis observed over periods up to 2 years. Hypercholesterolemia was present in all of the group on one or more occasions. In 17 of the 18 patients the cholesterol value exceeded 400 mg. per 100 cc. In 10 of these the value exceeded 600 mg. per 100 cc.

The authors are indebted to the Department of Pathology of the Presbyterian and Babies' Hospitals for the privilege of using their records.

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INSTANCES OF DISAGREEMENT IN THE RESULTS OF TWO TYPES OF ORAL GLUCOSE TOLERANCE TESTS.

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IN the course of performing 160 2-dose, 1-hour glucose tolerance tests (Exton-Rose^{4a} procedure) it seemed that this test was more sensitive than the conventional 1-dose test. It is the purpose of this paper to present selected instances where the 1-dose, 2-hour and the 2-dose, 1-hour glucose tolerance tests were performed on the same individual in order to determine the relative merits of the two tests and evaluate proposed criteria for their interpretation.

A review of the literature reveals three papers dealing with a comparison of the 2-dose and the 1-dose tests.

Kelly, Beardwood, and Fowler⁹ found the two tests to be in close agreement and cite only 2 cases out of 50 where disagreement occurred when both tests had been performed in the same individual. These authors place their reliance in the 2-dose, 1-hour test. Young¹⁸ studied 4 individuals with presumably normal carbohydrate metabolism and found the 2-dose test to be abnormal in each instance whereas the conventional 1-dose test resulted normally. He felt that the 2-dose test was in error. Brown¹ reported the results of both tests performed in each of 24 subjects. He considered the two tests to be equally accurate.

Methods. Individuals were selected upon whom we had obtained borderline or slightly abnormal 2-dose tests, that is, a 1-hour blood sugar value of 160 mg. per 100 cc. or more by the analytical method of Folin and Malmros.⁵ At the time of study none of the group was overweight, arteriosclerotic, or suffering from an infection. As far as could be determined, no other factor which might have influenced the glucose tolerance was operative. All of the individuals used in this study except Cases 13 and 14 are well known to us and have had other studies of their glucose metabolism made. Three individuals were known to have had glycosuria with a normal glucose tolerance for a number of years. All of the subjects studied were in good health and without past history or symptoms of diabetes except in Cases 6 and 16, who were suspected of having latent diabetes. Care was taken to provide for an adequate antecedent diet since it has been shown by Sweeney,¹⁴ Conn² and others that antecedent diet markedly affects glucose tolerance, and by Sweeny, Muirhead and Allday¹⁵ and Langner and Fies^{10a} that a diet inadequate in carbohydrates influences the 2-dose test as well as other glucose tolerance tests.

These selected individuals were also subjected to the conventional 1-dose, 2-hour technique in which a single dose of either 50 or 100 gm. of glucose was administered (Table 1). Our criterion for a normal response to this test requires that the fasting blood sugar shall be less than 120 mg. per 100 cc., the $\frac{1}{2}$ -hour value shall be 180 or less, and the 2-hour value for venous blood sugar shall be 120 mg. per 100 cc. or less. These criteria are commonly used in insurance practice. Even if the critical 2-hour level is reduced to 110 mg. per 100 cc. it would not cause any difference in the interpretation of the results in Table 1. For a discussion of these criteria we refer the reader to McCrudden,¹¹ Joslin,⁸ Exton and Rose,⁴² and Watson.¹⁷

Both types of glucose tolerance tests were performed in the morning after an overnight fast. In 10 of the cases we were able to obtain simultaneous samples of capillary blood from the finger and venous blood from the antecubital vein. In these cases duplicate determinations were performed on each sample of capillary and upon each sample of venous blood by the method of Folin and Malmros. The average of the duplicates in each instance is recorded in Table 1. In the other 6 subjects only capillary or only venous blood was obtainable as will be seen upon consulting Table 1.

Criteria for the Interpretation of the 2-Dose, 1-Hour Glucose Tolerance Test. According to the criteria of Exton and Rose,⁴³ a normal response required: 1, a normal fasting blood sugar; 2, a rise which did not exceed 75 mg. per 100 cc. in the $\frac{1}{2}$ -hour specimen; and 3, a 1-hour blood sugar value which did not exceed the $\frac{1}{2}$ -hour value by more than 10 mg. per 100 cc. We feel that their criteria were too strict in limiting the allowable rise during the second $\frac{1}{2}$ -hour to 10 mg. per 100 cc.

Gould, Altshuler, and Mellen⁷ showed that a 30 mg. per 100 cc. rise could occur during the second $\frac{1}{2}$ -hour in a normal individual. Their other requirements were a normal fasting blood sugar level and a rise during the first $\frac{1}{2}$ -hour not in excess of 50 mg. per 100 cc. These authors concluded that if at least two or the three requirements were fulfilled the individual could be considered as normal.

Cooperstock and Galloway³ found that in normal children a total rise of 80 mg. per 100 cc. could occur in 1 hour when capillary blood was employed.

Matthews, Magath and Berkson¹³ found that the 1-hour blood sugar value served as the most useful criterion and they did not depend upon the rise or fall pattern of the curve. Their critical level was established as 158 mg. per 100 cc. at the end of 1 hour when samples of venous blood were obtained and analyzed by the method of Folin and Wu. Below this level none of the individuals studied were diabetic. When the hour blood sugar level was between 160 and 180 mg. per 100 cc. the case was considered borderline since blood sugar values in 5.1% of normals and 7.7% of very mild diabetics studied by these authors fell into this range. When the 1-hour value was in excess of 180 mg. per 100 cc. all the individuals observed proved to be diabetic.

We accepted the critical 1-hour level of Matthews *et al.*¹³ because it diagnosed all of our causes of diabetes correctly, whereas the

criteria of Gould *et al.*⁷ failed to make the correct diagnosis of diabetes in 4 cases observed by us. The highest 1-hour value in our series obtained in the case of a presumably normal individual was 192 mg. per 100 cc.

TABLE 1.—COMPARISON OF BORDERLINE GLUCOSE TOLERANCE TESTS.

		Conventional 1-dose, 2-hour technique.					Exton-Rose 2-dose, 1-hour technique.				
	Sub- ject.	Date.	Fasting, mg. per 100 cc.	$\frac{1}{2}$ -hour, mg. per 100 cc.	2-hour, mg. per 100 cc.	Glyco- suria, at 2 hr. %.	Date.	Fasting, mg. per 100 cc.	$\frac{1}{2}$ -hour, mg. per 100 cc.	1-hour, mg. per 100 cc.	Glyco- suria, at 1 hr. %.
1	L. D.	7-30-41	v 80 c 80	150 180	60 60	3.0	7- 3-41	v 100 c 95	163 190	180 230	4.0
2	J. G.	5-27-41	v 112 c 112	180 200	102 107	1.5	6-17-41	v 117 c 115	190 220	175 225	2.5
3	J. S. P.	4-28-41	v 113 c 110	175 190	100 95	Neg.	4-24-41	v 106 c 104	152 154	192 222	Neg.
4	J. R.	8- 1-41	v 85* c 95*	125 145	105 95	0.5	7-30-41	v 98 c 93	135 142	160 190	No report
5	E. B.	6- 2-41	v 97 c 100	176 190	123 123	1.0	6-23-41	v 90 c 90	170 173	180 190	2.0
6	H. R.	8-11-41	v 102* c 97*	176 198	189 197	5.0	6-16-41	v 92 c 95	160 165	166 178	1.0
7	W. M.	8-13-41	v 88* c 90*	155 168	105 112	Neg.	8-27-41	v 88 c 88	175 185	190 200	0.5
8	H. L.	6-11-41	v 100 c 102	130 164	125 145	Neg.	8-25-41	v 95 c 98	152 165	175 182	Neg.
9	J. P.	8-28-41	v 90* c 107*	150 186	95 115	Neg.	9- 4-41	v 85 c 90	150 155	160 181	Neg.
10	R. G.	11- 6-41	v 98*	173	115	0.5	10-30-41	v 82 c 85	155 174	175 210	0.3
11	R. O.	10-16-36	v 85	175	100	No report	4- 2-35 6-25-36	c 125 c 92	225 148	235 160	0.3 0.3
12	K. B.	3-25-40	c 70	145	75	Neg.	1-16-40 6-17-40	c 85 c 97	185 160	185 180	0.3 0.5
13	D. A.	11- 2-40	v 82* c 86*	128 192	81 114	Neg.	10-29-40	c 97	130	173	Neg.
14	R. C.	11-17-36	v 87*	118	72	Neg.	11-27-36	c 95	155	180	Neg.
15	A. B.	2-14-35	c 97	137	106	Neg.	2- 7-35	c 112	145	187	Neg.
16	D. C.	5-30-40	v 132	156	176	No report	5-22-40	c 110	150	175	2.0

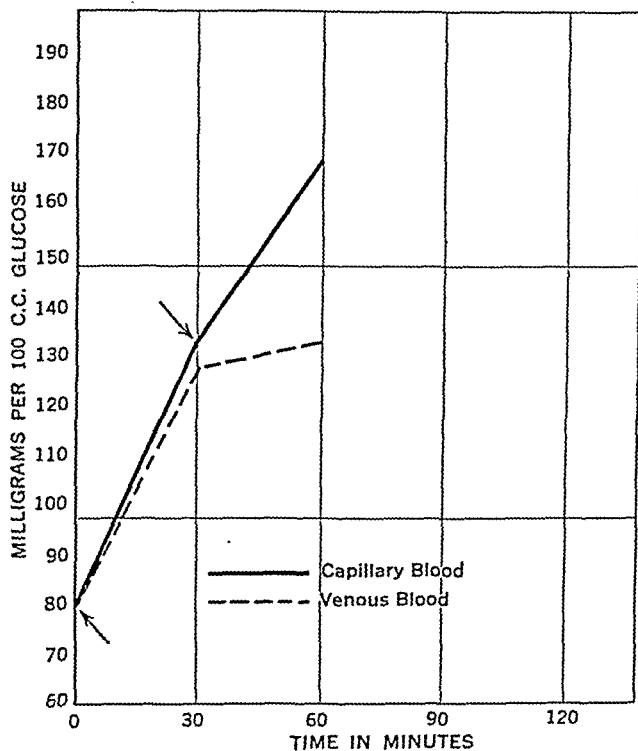
v = venous blood glucose value. c = capillary blood glucose value.

* These subjects received 100 gm. of glucose in 325 cc. of water. All others received 50 gm. in 200 cc. of water.

Interpretation of Capillary Blood Values. Frequently in life insurance practice and in some clinical laboratories, capillary blood is employed instead of venous blood. We use venous blood by preference but the results obtained on capillary blood are included

in this paper as a matter of interest in some cases and because only capillary blood values were available in other cases.

The interpretation of results obtained on capillary blood is difficult, as one can surmise from the studies of Foster⁶ and others, and it has been shown by Langner and Fies^{10b} that when the results are not within normal limits, 2-dose tests on capillary blood may be misleading due to the unpredictable capillary-venous difference. This difference may be negligible or it may be over 50 mg. per 100 cc. This variation is not consistent and cannot be taken into account by any formula or selected conversion figures. Figure 1



Each arrow indicates the ingestion of 50 gm. of glucose.

FIG. 1.—Capillary-venous difference during the Exton-Rose procedure.

is included to illustrate the significant difference which may occur between simultaneous capillary and venous blood sugar values during the 2-dose test. Too often, the source of blood, whether it be capillary or venous, is not taken into account despite the fact that this may make a great deal of difference in the interpretation of results.

Results. In Table 1, even if one discounts the results obtained on capillary blood as misleading or unreliable, there are comparative figures on venous blood (designated v in Table 1) for each type of

glucose tolerance test. Let us confine our attention to the venous blood sugar values for the 2-dose test in the first 10 cases. According to the criterion of Matthews *et al.*¹³ 2 subjects would be considered diabetic, 8 borderline, and none normal. According to the criteria of Gould *et al.*⁷ all 10 individuals would be considered normal. According to the 1-dose test 7 subjects would be considered normal, 2 borderline, and only 1 diabetic. This comparison is summarized in Table 2.

TABLE 2.—SUMMARY AND INTERPRETATION OF RESULTS IN CASES 1 TO 10
IN TABLE 1.

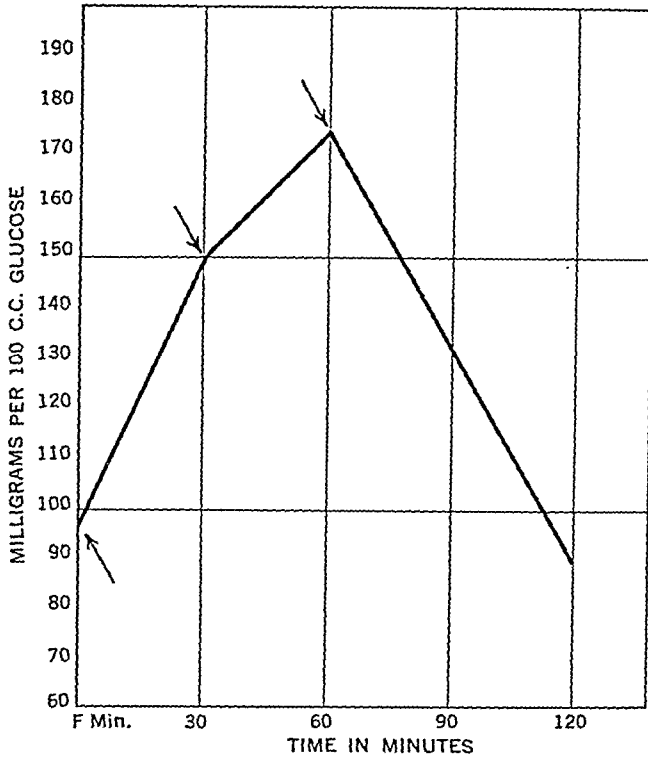
	Normal.	Borderline.	Abnormal.
<i>1-Dose Test.</i>			
Venous blood sugar values	7	2	1
<i>2-Dose Test.</i>			
Venous blood sugar values—criteria of Matthews <i>et al.</i>	0	8	2
Venous blood sugar values—criteria of Gould <i>et al.</i>	10	0	0

In the last 6 cases of Table 1 only capillary blood sugar values are available for the interpretation of the 2-dose test. From our experience with capillary blood we would consider the first 2-dose test performed upon R. O. to be borderline, whereas the later test is normal. The tests in Cases 12 to 16 are all in the borderline range. According to the 1-dose test, Cases 11, 12, 13, 14 and 15 are clearly normal while Case 16 is diabetic. Case 15 (A. B.) first observed in 1935 (Table 1) is now a diabetic requiring insulin. Case 16 (D. C.) since his borderline 2-dose test in 1940 (Table 1) has been considered to be a mild diabetic.

To summarize the results we may say that in 3 out of 16 cases a borderline 2-dose test has accurately diagnosed diabetes; in 2 of these instances the 1-dose test was in agreement. In 13 cases an abnormal or borderline 2-dose test has occurred in presumably normal individuals; in 2 of these instances the 1-dose test was also borderline.

In 4 instances of borderline 2-dose tests we have augmented the test by giving a third dose of 50 gm. of glucose at the end of 1 hour. A representative result is depicted in Figure 2. In each instance a fall of the blood sugar value occurred following the third dose of glucose. It is highly probable, however, that the third dose of glucose has little or no influence on the configuration of the curve, in view of the fact that Warren, Karr, Hoffman, and Abbott¹⁶ found the maximum rate of absorption of glucose from the gastro-duodenal unit to be 43.2 gm. per hour and usually it was considerably less than this. The first two 50-gm. doses in our 3-dose test would have been more than adequate to supply all the glucose that could have been absorbed in 2 hours so that the third 50 gm. would not be expected to cause additional absorption.

Subject H. V. L.
Three-Dose Test



Subject R. E. G.
Two-Dose Test

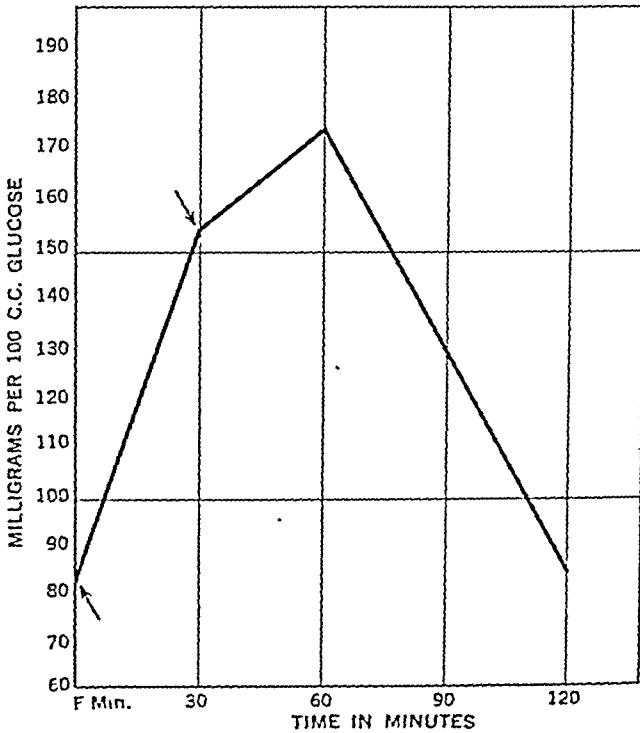


FIG. 2.—The response to multiple doses of 50 gm. of glucose given at $\frac{1}{2}$ -hour intervals.
Each arrow indicates the ingestion of 50 gm. of glucose.

A second glucose tolerance curve is depicted in Figure 2 in which the Exton-Rose procedure is extended for 2 hours without the giving of a third 50 gm. of glucose. It will be seen that the two curves in Figure 2 are very similar whether 2 or 3 doses of glucose are given. This is not surprising since MacLean and de Wesselow¹² found that additional large doses of sugar given during the height of absorption failed to raise the blood sugar above the previous level. A pertinent question to which we plan to devote further study is a comparison of the effect of giving glucose in a single dose of 100 gm. or in divided doses upon the configuration of the resultant curves in the same individuals.

Comments. The results presented indicate that the 2-dose glucose tolerance test of Exton and Rose is usually more sensitive than the 1-dose test. We may draw one of two conclusions: either the 2-dose test is more accurate than the 1-dose test in detecting potential diabetes, or the 2-dose test is oversensitive and may be used as an exclusion test but in borderline cases should be rechecked by performing a conventional 1-dose test.

At this point we are inclined to believe that the 2-dose test of Exton and Rose possesses greater sensitivity but that the conventional 1-dose test is more specific for diabetes.

We have accepted the criterion of Matthews *et al.*¹³ in interpreting our studies on the 2-dose test. Their criterion is more sensitive but less specific than the criteria of Gould *et al.*⁷ We think it is wise to err on the side of safety and accept the more sensitive criterion. In accordance with this point of view, any individual with 1-hour blood sugar value in excess of 160 mg. per 100 cc. by the analytical method of Folin and Malmros or by the method of Folin and Wu should be suspected of having diabetes until proven otherwise. It is apparent from our study that there is a borderline range between 160 and 190 mg. per 100 cc. where the results may indicate either a normal state or diabetes; in this range prolonged observation may be necessary.

It is obvious from the results of the above discussion that the incidence of disagreement between the 2-dose and the 1-dose tests will depend partly upon the criteria used in interpreting these tests. Had we adopted the criteria of Gould *et al.* we should have considered the 1-dose test more sensitive than the 2-dose test.

In addition to the study which led to the establishment of the criteria of Matthews *et al.*¹³ for the 2-dose, 1-hour glucose tolerance test, Dr. M. W. Matthews has also reviewed a large number of conventional 1-dose glucose tolerance tests at the Mayo Clinic and he has indicated to us in a personal communication that he considers the Exton-Rose procedure to be more accurate than the conventional 1-dose test in detecting diabetes, provided that the criteria established by Matthews *et al.*¹³ are followed.

High diagnostic accuracy has been claimed for the Extton-Rose test in several series of cases.^{4b,7,9,13} Our experience seems exceptional in that we have been able to find 13 cases out of 160 that have given what we consider to be borderline or abnormal Extton-Rose test when the 1-dose test and the clinical data suggest a normal carbohydrate metabolism. The above-mentioned 13 cases do not represent the total number of borderline Extton-Rose tests obtained in 160 consecutive tolerances. Additional instances of equivocal results were observed but only 16 could be studied sufficiently to supply material for this paper. It seems worthwhile to present our material because it demonstrates that the problem of interpreting the Extton-Rose glucose tolerance test is not infrequently just as difficult as the interpretation of the conventional 1-dose test, and because it indicates the need for more observation of the Extton-Rose test before final conclusions can be made regarding criteria, sensitivity and specificity.

Summary. From a group of 160 subjects who had submitted to the 2-dose, 1-hour glucose tolerance test, 16 cases are presented in which the results were borderline or slightly abnormal. A 1-dose test was also performed on these individuals. In 13 instances the 1-dose test and the available clinical data indicated a normal carbohydrate metabolism and therefore were in disagreement with the 2-dose glucose tolerance test. We believe that the conventional 1-dose glucose tolerance test is more reliable than the newer Extton-Rose procedure.

We wish to acknowledge the technical assistance of Harry L. Fies.

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STUDIES OF SUBSTITUTED VINYL BARBITURIC ACIDS.*

II. THE CLINICAL USE OF SODIUM 5-ETHYL-5-(1-METHYL-1-BUTENYL) BARBITURATE (VINBARBITAL SODIUM).†

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IN an earlier paper⁸ detailed pharmacologic studies of 2 new substituted vinyl barbituric acids were described. These compounds were selected from a number synthesized by Cope and Hancock^{5a-c} by their method for introducing alkyl vinyl groups into malonic and cyanoacetic esters. In animals the 2 new compounds were found to be effective narcotics with favorable characteristics. The more promising of the 2 was 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid. It was found to have a comparatively wide margin of safety in rats and dogs and by comparison with isoamylethyl barbituric acid the "therapeutic index" of the new compound, as expressed by the LD50/AD50 ratio, was as great as, and perhaps greater than, that of the other barbiturate. The new compound also was found to be considerably less depressant to blood pressure upon intravenous and intraperitoneal injection in dogs than was the other barbiturate. Also some evidence was obtained indicating less profound depression of the respiratory center in decerebrate dogs from narcotic doses of the new barbiturate than from equivalent amounts of isoamylethyl barbituric acid. Only negligible amounts of narcotic material could be found in the urine of dogs after administration of anesthetic doses of the new compound. No significant degree of tolerance was developed in rats and dogs after repeated administration of the new drug and no toxic effects were observed in these animals which received repeated doses.

In view of the above findings, it was felt that the new barbiturate deserved preliminary clinical trial and the report of its administration as a sedative and hypnotic to approximately 100 patients was included in the earlier paper.⁸ Results were good and no unfavorable reactions were observed. It is the purpose of this communication to report observations during more extensive clinical study of the compound. In addition to evaluating the usefulness of the barbiturate, the chief object of this study has been to watch for

* The first paper of this series was not numbered. It appeared under the title Studies of 2 New Substituted Vinyl Barbituric Acids (Ref. 8 in the bibliography of this paper).

† Vinbarbital sodium is the non-proprietary name which has been recognized by the Council on Pharmacy and Chemistry for this compound. The vinbarbital sodium used in this study was supplied by Sharp & Dohme under their trademarked name, "Delvinal Sodium."

toxic effects and undesirable reactions which might appear in a fairly large series of patients receiving the drug.

Following the favorable preliminary trial mentioned above the use of the new drug was continued at the Duke University Hospital. The sodium salt of 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid (vinbarbital sodium) was administered in capsules by mouth to patients who needed an hypnotic or sedative. No attempt was made to use the new compound to the exclusion of other barbiturates and no restrictions were imposed upon the random selection of the cases, except precautions ordinarily observed in giving barbiturates.

During a 12-month experimental period, a total of 423 patients received the new barbiturate. The cases have been divided into five groups according to the number of doses each patient received. Those in Group I received only 1 dose and represent chiefly patients who needed only a single dose of an hypnotic while in the hospital. Many of these were in for a short stay. Also included are some cases in which a single dose was given for sedation before some minor procedure, such as sternal puncture or lumbar puncture. Patients in Group II received 2 to 5 doses, those in Group III 6 to 10 doses, Group IV 11 to 20 and Group V more than 20 doses. To the above series of 423 cases have been added 42 others collected after the first 12-month period but followed carefully because of some point of special interest in the case. These have been divided among the groups in the same manner. Because the medical service on which the drug was used is a very active one, with rapid turnover of patients, the opportunity was not available for long-continued administration of the drug in the majority of patients. However, a considerable number of cases is included in Groups IV and V and most of those in Group V received comparatively large amounts of the drug.

Patients who received the new barbiturate were observed for evidence of undesired or toxic reactions, such as excessive depression, undue persistence of drowsiness, excitement, nausea, dermatitis, and so on. In addition, the case record of every patient was reviewed in a search for possible toxic effects. In most patients who received more than 1 dose of the drug, blood counts and urinalyses done before and after the administration of the drug were compared in looking for evidence of hemolytic anemia, suppression of bone marrow activity or irritation of the kidneys which might have been caused by the barbiturate. This information was available on all cases in Group V, all except 3 in Groups IV and III and in 73% of cases in Group II. Failure to record the information after the drug was given in the rest of the cases in Group II usually was due to the brief duration of the patient's stay in the hospital. Blood and urine examinations were checked, if recorded, before and after the drug on patients in Group I (who had only 1 dose) and all

of the case histories were reviewed so that any important toxic reaction would have been detected.

Table 1 presents a summary of the cases used, divided according to diagnosis, and indicates the number of cases of each general diagnosis included in the various groups mentioned above. In the interest of brevity diagnoses have been stated in general terms and cases have been classified only according to the chief condition or disease.

TABLE 1.—ANALYSIS OF CASES USED.

Diagnosis.	Number of cases in each group.					Total.
	I.	II.	III.	IV.	V.	
Asthma and allergic states (except skin conditions)	7	10	2	3	4	26
Diseases of the blood (including anemias, leukemias, etc.)	14	12	1	3	..	30
Diseases of bones, joints and cartilage (including arthritis)	3	12	4	1	1	21
Deficiency states	1	5	1	7
Diabetes mellitus	7	11	1	1	1	21
Fevers	8	2	1	..	1	12
Fungus diseases	1	1	..	2
Gall bladder diseases	4	4	..	2	..	10
Diseases of heart and blood-vessels	21	24	5	5	5	60
Diseases of kidney and urinary tract	3	2	3	8
Lead poisoning	1	1
Liver diseases	1	3	1	1	..	6
Lung diseases (except tuberculosis)	7	13	1	2	..	23
Diseases of the nervous system (including psychoneurosis)	23	31	2	2	1	59
Skin diseases	6	6	2	1	..	15
Diseases of stomach and intestines	14	5	3	4	1	27
Syphilis	10	8	1	1	6	26
Diseases of throat and nose	3	7	2	12
Thyroid diseases (chiefly hyperthyroidism)	5	14	3	3	19	44
Tuberculosis	7	6	4	3	1	21
Tumors (benign and malignant)	6	10	5	4	1	26
Diagnosis deferred	3	5	8
Total	155	190	41	37	42	465

Dosage and Uses. For medical patients vinbarbital sodium has been given in doses of from 32 mg. ($\frac{1}{2}$ gr.) to 0.2 gm. (3 gr.). The average dose and the one used in the great majority of cases was 0.1 gm. ($1\frac{1}{2}$ gr.). Single doses of more than 0.2 gm. (3 gr.) have been given therapeutically only on rare occasions in our series. However, in studying the effect of the drug on blood pressure, respiration and heart rate (as described below), a number of patients were given 0.3 gm. ($4\frac{1}{2}$ gr.) as a single dose, without harmful effects. In cases where profound sedation was desired 0.2 gm. doses were repeated at intervals of about 2 hours until the desired effect was obtained. The largest amount so given in 24 hours was 1.4 gm. (21 gr.) to a patient with extensive chronic bronchitis and intractable asthma.

It is felt that average doses mentioned above are quite conservative and that with proper precautions larger doses could have been used with safety if they had been indicated. Indeed, Davidoff⁶ and Davidoff and Goodstone⁷ have reported the frequent use of doses of the order of 0.3 to 0.6 gm.

(4½ to 9 gr.) in disturbed patients without significant untoward effects. Occasionally they gave, in divided doses, amounts to 2 gm. (20 to 30 gr.) in severely excited individuals. of very large doses of this or similar compounds should be undertaken only under conditions permitting careful observation of the patient and only by those familiar with the management of possible complications.

The widest use of the drug on the medical wards has been for administration at bedtime as an hypnotic to patients with simple insomnia. Here the dose usually was 0.1 gm.; occasionally 64 mg. (1 gr.) or 0.2 gm. The smaller doses were repeated after 2 to 3 hours, if the first dose was not effective or of too short duration.

A number of patients in need of continued sedation also have been given vinbarbital sodium in doses ranging from 32 mg. 2 or 3 times per day, in mildly nervous individuals, to 0.1 gm. 3 or 4 times per day in cases of severe hyperthyroidism. Perhaps special mention should be made of this later usage. Twenty-two cases of hyperthyroidism received the drug in repeated doses, particularly postoperatively, for the control of nervousness and as an adjunct to other standard therapeutic measures. The dosage employed usually was that mentioned above but occasionally 32 mg. t.i.d. and 0.1 gm. at night was sufficient. Results were gratifying, especially in 3 very severe cases where the control of nervousness and hyperactivity was of utmost importance. It was the particular observation of both the medical and surgical attendants that these symptoms were controlled adequately without the production of undue depression or somnolence. None of the cases showed any indication of toxic effects of the drug. Fifteen other less severe cases of hyperthyroidism received the new barbiturate in smaller doses.

To allay anxiety, and as sedative preparation for minor procedures, such as lumbar puncture or sternal puncture, doses of 0.2 gm. have been given about 1 hour before the procedure was to begin. It is preferable in such instances to allow 1 hour for the full development of the effect of the drug.

Vinbarbital sodium also has been used in conjunction with coal-tar analgesic drugs to increase the effectiveness of the latter in relieving pain. Here the dose has been 32 mg. to 0.1 gm., together with the usual dose of salicylate or phenacetin, and the combination is particularly effective in combating mild or moderately severe pain associated with considerable nervous tension. No attempt has been made to relieve pain with vinbarbital sodium alone, because it is not to be expected that such a drug will have pronounced analgesic effects unless given in comparatively large doses, as in obstetric amnesia.

Results. The results of experience with the new barbiturate may be summarized briefly by the statement that the drug has been found to be an effective hypnotic and sedative with very desirable characteristics; and that few unfavorable reactions have occurred following its use.

In observing the patients and reviewing the case histories summarized in Table 1, particular search was made for unexplained falls in hemoglobin, red cells or white cells in the blood; the occurrence of purpuric manifestations; and the appearance of albumin, casts or red cells in the urine, following the use of delvinal sodium. All cases showing a fall in hemoglobin of more than 10% were investigated but in every instance the fall was readily explainable on the basis of the patient's disease. No cases receiving the drug

developed leukopenia or evidence of thrombocytopenia, and 1 patient with preëxisting leukopenia received it as a sedative without exaggeration of the condition. No abnormalities in the urine, which had not been present previously, were found following the drug.

Evidence of the development of toxic hepatitis following the new barbiturate also was sought for but not found in any case. Three patients with such liver damage due to sulfonamide drugs received vinbarbital sodium without evidence of harm from it. One of these patients, who also had Hodgkin's disease, died after leaving the hospital. The other 2 recovered before discharge. It should be mentioned that the effect of barbiturates is apt to be increased in the presence of liver damage^{3,9,10} and that they must be used with due caution under such circumstances.

Concerning untoward effects of the drug comparatively little can be said because of the scarcity of such reactions. The nearest approach to a serious reaction was in a 66-year-old white widow with generalized arteriosclerosis, arteriosclerotic heart disease with auricular fibrillation, pernicious anemia, diabetes mellitus and chronic cystitis. Approximately 10 hours after 0.1 gm. of the drug the patient was slightly confused and probably dizzy, because she fell while getting out of bed. However, she had received for the cystitis, 1.8 gm. of sulfanilamide per day for $3\frac{1}{2}$ days before the dose of barbiturate was given. In view of the time intervals and the well-known effect of sulfanilamide in causing confusion, dizziness, and so on, it seems probable that it was the chief offender in this case. However, it has been reported that barbiturates are rendered more toxic by sulfanilamide^{1,2} and it is possible that the small dose of the barbiturate may have contributed to the reaction because of the simultaneous administration of sulfanilamide. It may be mentioned at this point that patients receiving sulfonamides may be more susceptible to the action of barbiturates.

One 27-year-old white male developed an itching vesicular and papular rash, associated with mild pharyngitis, at first thought to be chickenpox, later regarded as "possibly a drug eruption"; 2 days after the second of 2 consecutive nightly doses of 0.1 gm. of vinbarbital sodium. The rash cleared within 3 to 4 days and its nature was not definitely determined. The patient had received atropine 2 days before and atropine and prostigmine on the day the rash appeared. This may represent a case of drug rash due to vinbarbital sodium, but the evidence is inconclusive. No other similar cases were observed. The drug was used for sedation in a number of cases of skin diseases with exaggeration of symptoms in only 1 case. This was a 41-year-old white man with severe dermatophytosis of the feet and extensive dermatophytid reaction. There was a moderate flare-up of the latter process, with increased itching, following a single dose of 0.3 gm. ($4\frac{1}{2}$ gr.) of vinbarbital sodium which was given to observe the effect on blood pressure, and so on,

as reported below. It was discovered later that the patient had reacted similarly to phenobarbital.

Excitement was not observed following the use of vinbarbital sodium and only 1 abnormal psychic reaction was seen. It is unlikely that this was related to the drug. A psychoneurotic, 39-year-old white spinster, who was prone to have hysterical attacks, received 0.2 gm. of the drug for sedation at night following lumbar puncture. She slept during the night but was found the following morning in a detached mental state which the psychiatric consultant viewed as an episode of dissociation hysteria. It was his opinion that this represented an exaggerated reaction related to the patient's hysterical tendencies, probably precipitated by the lumbar puncture, and that the use of the barbiturate was only incidental. The patient returned to her normal state after about 8 hours.

It is recognized that excitement is not likely to occur following barbiturates among patients such as were used in this study. However, the freedom from reactions of this type in our cases has been gratifying and Davidoff and Goodstone⁷ have reported comparatively few untoward reactions in psychiatric patients who were treated with vinbarbital sodium. Nausea or other gastro-intestinal complications were not observed in our patients following the drug.

There was no clinically detectable evidence of habituation to the drug under the conditions of hospital administration. It was given to some patients who required repeated sedation with it or some other sedative; but nothing was seen to indicate any special attachment to or craving for this particular drug in any of the patients. So far as could be determined tolerance was not developed. When the barbiturate was given repeatedly as an hypnotic to patients with simple insomnia the dose was not increased after repeated administration and we were not able to detect that the drug lost its effectiveness in these cases. However, our cases were not well suited for investigation of tolerance because the drug was not continued for long periods of time in most of them. Davidoff and Goodstone⁷ have reported less tolerance to vinbarbital sodium after repeated administration than to two other commonly used barbiturates. These observations are in accord with the findings reported in the previous paper,⁸ concerning the relative lack of tolerance in rats and dogs, as judged by the average dose of the drug necessary to continue to narcotize the majority of a group of animals after repeated administration. However, Carmichael and Thompson⁴ have reported a decrease in the sleeping time of guinea pigs after repeated administration of a fixed dose of vinbarbital sodium.

Considerable clinical experience with the drug has produced the impression, consistent with the results of experimental work in animals, that vinbarbital sodium definitely belongs to the group of so-called "short-acting"¹¹ barbiturates. On the basis of both experimental and clinical observation, it appears that its action is of shorter

duration than that of sodium amytal. In addition, while reliable comparative clinical information is difficult to obtain, the definite impression has been gained from observation of patients that in average dosage the new drug also is briefer in its effects than sodium pentobarbital.

The induction of sedation with vinbarbital sodium appears to be somewhat slower than with sodium pentobarbital. The induction time for sleep, when the drug is given about 3 to 4 hours after the evening meal, usually is of the order of 30 to 35 minutes. Induction appears to be quite gradual and patients have not complained of the "drugged sensation" during induction with this drug which occasionally is experienced with other commonly used barbiturates. The absence of this sensation, after taking vinbarbital sodium, has been the subject of spontaneous comment by several individuals with better than average powers of observation, who were asked to try the drug and who usually had experienced the sensation after other barbiturates.

When vinbarbital sodium is given at bedtime to patients with simple insomnia who have no stronger stimuli than nervousness or mild anxiety to keep them awake, and whose chief difficulty is in going to sleep, the usual experience is that they will sleep until awakened the following morning by the activities of the ward. In patients who have some definite discomfort or stimulus which might be expected to awaken them when the sedative effect of the drug reaches a low level; sleep usually lasts, with average doses, for 3 to 5 hours, there being, of course, much variation among individuals. Greater duration of action results as the dose is increased.

Persistence of drowsiness beyond the time of normal awakening, or "hangover," following average doses has been so rare as to make doubtful the significance of the subjective sensations of this type described by the few patients who have mentioned them in response to leading questions. Such symptoms undoubtedly have been present when patients were awakened within 2 to 3 hours after receiving the drug and prevented from going back to sleep by examinations, treatment, and so on; and in individuals who were given repeated doses with the deliberate purpose of producing prolonged sedation.

Effect on Blood Pressure, Pulse and Respiration. To observe the effect of the new barbiturate on blood pressure, pulse and respiration 25 patients in good general condition were given larger than average doses and followed with care for $2\frac{1}{2}$ to 3 hours, or until any depression which had been observed largely had disappeared. The doses used for routine administration were so small as to make unprofitable an attempt to follow in this fashion every patient who received the usual therapeutic dose of 0.1 gm. The 25 patients were given at 1 dose 0.2 or 0.3 gm. (3 or $4\frac{1}{2}$ gr.), roughly according to body weight, and readings were taken at intervals of $\frac{1}{2}$ hour. Fourteen

patients received 0.2 gm. and 11, 0.3 gm. There was no significant difference in the two groups. After the drug was given the mean change in blood pressure in mm. of mercury for the 25 patients was: at 1 hour, -3 systolic and -3 diastolic; at 2 hours, -5 systolic and -4 diastolic; and at 2½ or 3 hours (all except 6 followed 3 hours), -3 systolic and -2 diastolic. In only 4 cases was there observed a fall of more than 10 mm. of mercury at any time and in only 2 or more than 20 mm. (24 and 22 mm. respectively). Both of the latter were in patients who had been made apprehensive by the repeated blood pressure readings to establish a base line before the drug was given and whose starting pressure, therefore, was above their normal range.

The mean change in pulse rate per minute was: at 1 hour, -2; at 2 hours, -5; and at 2½ or 3 hours, -4. In no case was there observed abnormally fast or unusually slow heart rate following the drug.

The average respiratory rate did not change at 1, 2 or 3 hours following the drug and no significant change of rate was observed in any patient. It is believed that there was no change in blood pressure, pulse or respiration in any of the 25 patients which would indicate undue depression by vinbarbital sodium. Nor have we observed any other evidence of such untoward effect from doses of the drug which have been needed in our patients. Davidoff and Goodstone⁷ in giving large doses of barbiturates to excited patients observed more frequent lowering of systolic blood pressure, but much less frequent respiratory depression, with vinbarbital sodium than with sodium amytal or pentobarbital sodium.

Pathologic Studies. Seventeen patients who received vinbarbital sodium died in the hospital and 2 are known to have died after discharge. Autopsy was performed in 11 of these cases. Only 3 patients who died received more than 5 doses of the drug, 1 receiving 6, another 7 and the other 21. Deaths were due to a variety of causes but all were readily explained by clinical or autopsy findings. Careful review of the case history in every case failed to furnish any evidence that the drug contributed in any way to the fatal outcome.

In addition, the writer is indebted to Dr. D. H. Sprunt for reviewing the histologic sections of the organs of 10 autopsies (1 autopsy was done outside the hospital and the material was not suitable for microscopic examination). No abnormalities were found in any case which could be interpreted as due to toxic effect of the barbiturate.

Summary. A new barbiturate (vinbarbital sodium), which showed very favorable characteristics during experiments on animals, has been administered to a series of 465 patients under hospital observation. The compound was found to be an effective sedative and hypnotic when used in a wide variety of disease states. No serious and few undesirable reactions were encountered. The usual

dosage was from 32 mg. ($\frac{1}{2}$ gr.) to 0.2 gm. (3 gr.). The new drug belongs to the group of so-called "short-acting" barbiturates, its effect is gradual in onset, relatively brief in duration and seldom persists beyond the time of natural awakening. No significant effects on blood pressure, heart rate or respiratory rate were produced by larger than average doses. In 10 cases which came to autopsy after having received the new barbiturate, no lesions were found which could be interpreted as due to toxic effect of the drug.

Because of the results of animal experimentation and the experience described above during its administration to patients, it is believed that the new barbiturate represents a worthy addition to the list of sedative drugs available for clinical use.

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GASTROSCOPIC OBSERVATIONS IN PULMONARY TUBERCULOSIS.*

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It is well known that tuberculous enteritis is a common complication of cavernous pulmonary tuberculosis. Tuberculosis of the stomach, however, is very rarely found. Cullen¹ found at autopsy, that 70.4% of 1043 cases of pulmonary tuberculosis had tuberculous lesions involving the mucosa of the small intestine and colon; but was able to find only 4 cases of tuberculous involvement of the gastric mucosa. It should be pointed out, however, that gastric symptoms are not infrequently present in patients with advanced

* Opportunity to study these patients was made possible by the coöperation of the Tuberculosis Service.

TABLE 1.—ANALYSIS OF DATA.

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Patient.	Age.	T.B. status.*	Diagnosis secondary.	Sputum.		Gastric.		Duration (yrs.).	G.I. symptoms.	Gastroscopic diagnosis.
				For T.B. Amount.	For T.B. Acid.	For T.B. Acidity.				
W. C. W. C.	48	3B	Pul. fibrosis and emphysema	+	+	+	No res.	2-3	Anorexia	Normal stomach.
W. C.	61	1A		+	+	+	No res.	1	Anorexia; hematemesis	Normal stomach.
V. M.	78	3B	Tb. bronchus	+	+	+	No res.	4 (12)	None	Normal stomach.
L. R.	34	3B	Artif. pneumothorax	+	+	+	No res.	1	Gas distention (G.B. neg.)	Chr. supert. gastr. with hem.
G. L.	31	3B	Latent syphilis	+	+	+	No res.	1	Hematemesis, N. and V.	Chr. supert. gastr.
I. H.	21	3B	Chl. alcoholism	+	+	+	No res.	1	Anorexia	Chr. supert. gastr.
J. N.	38	3B	Chl. alcoholism	+	+	+	No res.	1	None	Chr. supert. gastr. with hem.
R. S.	36	2B	Artif. pneumothorax	+	+	+	No res.	1	Diarrhea (neg. G.I. roentgen ray)	Chr. supert. gastr.
T. G.	28	2B	Tb. enteritis	+	+	+	No res.	2	Vomiting, cramps, diarrhea	Chr. supert. gastr.
F. J.	43	3B	Tb. enteritis	+	+	+	No res.	20	Anorexia	Chr. atr. gastr.
T. McL.	21	3B	Tb. bronchus	+	+	+	No res.	9	None	Chr. atr. gastr.
J. E.	46	3B	Cure, alcoholism, pul. fib. and emphysema	+	+	+	No res.	1	Erectations; upper abd. distress	Chr. atr. gastr. gastr.; chr. supert. gastr. atr.
B. C.	47	3B	Tb. enteritis	+	+	+	No res.	1-1	None	Chr. atr. gastr.; chr. supert. gastr.; an-trial distortion.
B. N.	27	3C	Syphilis	+	+	+	No res.	1	Epigastric and low abd. pains	Chr. atr. gastr.; chr. supert. gastr.; (an-trial).
L. M.	36	3B		+	+	+	No res.	1	None	Chr. supert. gastr.; chr. atr. gastr.
J. F.	46	3B		+	+	+	No res.	1	Anorexia; constipation	Chr. supert. gastr.; chr. atr. gastr.
McC.	41	2B	Tb. enteritis (?)	+	+	+	No res.	1	Anorexia; vomiting	Chr. supert. gastr.; chr. atr. gastr.
W. G.	21	3B	Asthma and tb. laryngitis	+	+	+	No res.	1	Upper abd. pain unrelated to meals	Chr. atr. gastr.; chr. supert. gastr.
J. D.	49	3B	Seronegative syph. (treated)	+	+	+	No res.	1	Prev. intest. obstruction	Chr. supert. gastr.; chr. atr. gastr.
A. F.	38	2C	Laryngitis syph. artif. pneumo.	+	+	+	No res.	4	Cramps; diarrhea	Chr. atr. gastr.; chr. supert. gastr.
A. R.	29	2B	Phyct. conjunctivitis	+	+	+	No res.	4	Epigastric distress; tendent; distended; gas.	Chr. supert. gastr.
J. C.	40	2B	Tb. peritonitis	+	+	+	No res.	1	Cramps; constipation	Chr. supert. gastr.
J. F.	37	3B	Tb. bronchus, tb. enteritis	+	+	+	No res.	4	None	Chr. supert. gastr.
J. C.	41	3B	Silicosis	+	+	+	No res.	4	None	Chr. supert. gastr.
J. L.	27	2B	Tb. laryngitis; tb. enteritis	+	+	+	No res.	4	None	Chr. supert. gastr.
T. B.	42	2B	Drug addiction	+	+	+	No res.	4	None	Chr. supert. gastr.

* Tuberculous diagnosis: 1. Minimal. 2. Moderately advanced. 3. Far advanced. A. Asymptomatic. B. Minimal to moderate symptoms. C. Marked symptoms.

* Tuberculous diagnosis; symptoms.

pulmonary tuberculosis. He found that 29.3% of the patients had digestive disturbances. The gastric symptoms encountered consisted of anorexia, pain, nausea, vomiting and belching.

Renander,³ in a recent publication, reported 2 cases of proven tuberculosis of the stomach, and reviewed the small number of reported cases. It is notable that the majority of these develop on a basis of a hematogenous dissemination to the stomach wall, or, more frequently, to adjacent structures—particularly lymph nodes. There are not roentgenographic findings pathognomonic of tuberculosis of the stomach. Tuberculous lesions of the stomach may cause pyloric stenosis, in which case it is secondary to healing by fibrosis and cicatrization of an antecedent annular ulcerative lesion. They may resemble infiltrative neoplasms, as well as polypoid gastritis. No cases diagnosed by gastroscopy have been reported.

No gastroscopic observations in tuberculous patients have come to our attention. While the effect of a chronic debilitating disease on the gastric mucosa may be due to several factors, among them deficient absorption or increased requirement of vitamin, several questions of special interest arise in the tuberculous patient.

Materials and Methods. In this investigation 27 patients with pulmonary tuberculosis were gastroscoped. This study was undertaken in an effort to clarify three points: First—can a specific lesion be demonstrated in the stomach in late stages of pulmonary tuberculosis if the gastric mucosa is examined through the gastroscope? Second—what effect has the prolonged swallowing of purulent material on the gastric mucosa? Third—could the gastroscopic findings be correlated with the presence or absence of digestive complaints?

The patients selected for examination all had severe pulmonary disease of a few month's to 20 years' duration. Many were in the advanced stages of tuberculosis. The gastroscopist did not know whether gastric symptoms were present until the final tabulation of results was completed.

Results (Table 1). While none of the 27 patients examined was ambulant, and some were so weak that it was necessary to lift them from stretcher to examining table, 26 were successfully gastroscoped.

Entirely normal gastric mucosa was encountered in 5 patients. Chronic superficial gastritis was found in 7; chronic atrophic gastritis in 3; and a combination of these lesions occurred in 10 patients. Chronic hypertrophic gastritis was seen in only 1 patient. Ulcers, tumors and tuberculous lesions were not observed. Mucosal bleeding was seen in 3 of the patients with chronic superficial gastritis.

The 5 patients in whom normal gastric mucosæ were found had no gastric complaints except anorexia. Ten of the remaining 21 patients had diffuse involvement of the gastric mucosa of a moderate to marked degree, but only 3 had gastric symptoms, while 6 of the 11 patients with only patchy, mild to moderate mucosal involvement had gastric complaints.

Symptoms occurred in 6 of the 10 patients having both chronic

superficial and atrophic gastritis, in 2 of the 7 patients with chronic superficial gastritis, and in 1 of the 3 patients with chronic atrophic gastritis. The one patient with chronic hypertrophic gastritis had no gastric complaints.

The sputum varied in amount from scant to profuse, a moderate amount representing the average. Tubercle bacilli were present in the sputum of all but 3 patients. The fasting gastric contents usually were slight in amount, and 8 patients had no residue. Of the remaining 19 patients only 7 had free hydrochloric acid in the fasting specimen. In 9 patients the gastric residue was examined for tubercle bacilli which were present in 5, 3 of whom had free hydrochloric acid in the specimen.

Discussion. No apparent correlation between duration, severity, or type of tuberculosis and the presence of abnormalities of the gastric mucosa could be found. Neither could the amount of sputum produced be directly correlated with involvement of the gastric mucosa. The quantity of sputum swallowed could not be measured.

No specific gastric lesion was encountered gastroscopically. The absence of a specific gastric lesion is of particular interest since 5 of the patients had tuberculous enteritis. Chronic superficial gastritis was found in about double its incidence in patients with gastric complaints but no systemic disease.^{2,4} The progression of this mucosal alteration to chronic atrophic gastritis was seen in a correspondingly large group of patients. Whether these findings are caused by swallowed purulent material or general debility of the patients cannot be determined until comparable studies in other debilitating diseases are carried out.

Nine of 21 patients with gastroscopic evidence of abnormal mucosa had digestive symptoms, while none of the 5 patients with normal findings had such complaints. All of these patients had scant fasting gastric contents, and in only 7 of the entire series could free hydrochloric acid be found. The low incidence of gastric complaints in the patients with abnormal mucosæ may be explainable by the fact that all were at bed rest, most ate sparingly, and hydrochloric acid was frequently absent from the fasting gastric specimen. Cullen¹ reported an incidence of digestive symptoms of 21.7% in tuberculous patients without specific intestinal lesions. This relationship corresponds closely to our observations and the presence of non-specific gastritis may have been related to this portion of Cullen's¹ series.

Summary. Twenty-seven patients with pulmonary tuberculosis had gastroscopic examinations made.

No specific lesion was found, even though 5 patients had tuberculous enteritis. Chronic superficial gastritis was found alone and combined with chronic atrophic gastritis in an unusually large number of patients. The abnormalities of the gastric mucosa, how-

ever, could not be correlated with the duration, severity, or type of tuberculosis, nor with the quantity of sputum expectorated.

Gastric symptomatology failed to follow directly the gastroscopically demonstrated lesions; but this was thought to be influenced by bed rest, the reduction in food consumption caused by anorexia, and frequent absence of free hydrochloric acid in the fasting specimen.

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AN UNUSUAL CASE OF AMEBIC HEPATITIS.

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Case Abstract. A male, negro, elevator operator, aged 32, who was born in New Orleans and had lived in Mississippi until 1938, was admitted to this hospital, February 17, 1941. The chief feature of his past history was that his bowels usually moved 3 or 4 times a day; they were quite loose and occasionally contained bright red blood. Five days before admission he developed a head cold with some pain in his chest and abdomen. Later, the pain became sharp in the upper back, right flank and right lower quadrant, gradually involving the entire abdomen and radiating into the scrotum. There was no diarrhea, chills or urinary symptoms. Temperature on admission was 102°, his white blood count 14,000 and polys 66%. Urine contained albumin and an occasional red blood cell. There was marked tenderness in the right costovertebral angle extending around the flank to the right lower quadrant, associated with spasticity, but no rebound tenderness. The rectum was tender high up on the right side.

Films of the kidneys and urinary tract showed no abnormality. Analyses of urines subsequently were negative. A diagnosis of "appendicitis and possibly pyelonephritis" was made.

Laparotomy on the night of admission revealed no fluid in the abdomen. A pale but slightly injected appendix was removed (pathologic report normal). The mesenteric nodes were not enlarged. Culture of peritoneal fluid was sterile.

Subsequent Course. During the first few days after operation the temperature ranged between 101° and 102°. He vomited several times and his abdomen was distended. A Miller-Abbott tube was inserted, the Roentgen ray having shown marked distention of the jejunum and ileum with fluid level formation.

On the fifth day after operation his scleræ became icteric and there was considerable tenderness over the liver and right costovertebral angle and some bulging in the right upper quadrant. The history of loose stools, passage of blood, the presence of jaundice and tender liver suggested a stool hunt for amebæ, and these were found within a short time. At this time his temperature rose to 104°. There was dullness and diminished breath sounds over the right base, that is, signs of fluid, and marked tenderness over the right costovertebral angle and over the liver though the edge of this organ could not be felt.

Emetine hydrochloride, 0.06 gm., was begun 8 days after operation and continued for 2 weeks. During this period the temperature never rose above 101° , and tenderness of the liver had almost disappeared. Three days after stopping emetine the temperature rose to 104° and a second course, lasting 1 week, was instituted. Anayodin by mouth was also administered to destroy the intestinal parasites. Owing to relapse of fever a third course of emetine, lasting 15 days, was begun, and 54 days after operation 400 cc. of straw-colored, hazy fluid was withdrawn from the right pleural cavity. Guinea pig inoculation and culture of this exudate were negative. His convalescence from this point was gradual, but complete; repeated examination of stool was negative, and all physical signs of illness disappeared.

Discussion. Mistaking amebic intestinal disease for appendicitis is not new; it has been described repeatedly during the recent Chicago epidemic, and is probably due to ulceration of the cecum.

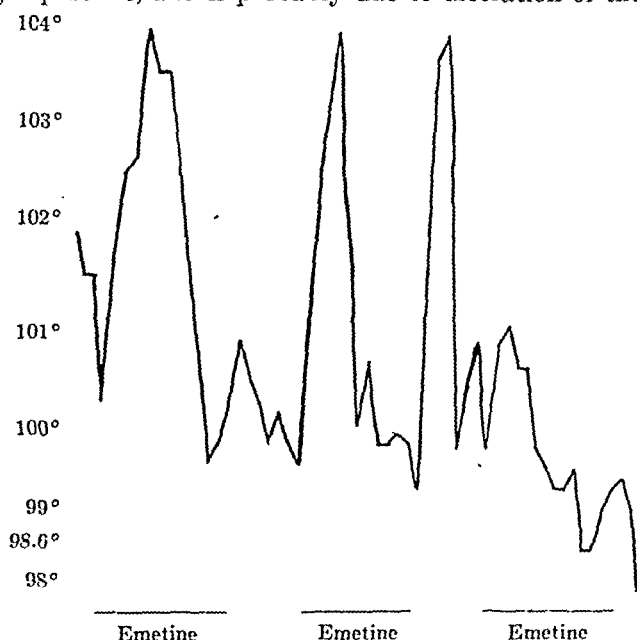


CHART 1.—The effect of emetine on the temperature in a case of amebic hepatitis.

The costovertebral tenderness and radiation into the groin and scrotum were probably due to pressure on or irritation of the right urinary structures by the diseased liver according to the urologic consultant. The intense jaundice is also rare in amebic disease of the liver. The late Professor O'Connor, who had a large experience with amebic liver abscess in the tropics, stated that jaundice in liver abscesses was rare. In this case the bilirubin reached 18 mg. per 100 cc. and was associated with a low phosphatase. The negative cephalin flocculation test is also remarkable.

The necessity for three courses of emetine is unusual. Ordinarily one course suffices, but as there was a prompt rise in temperature (see Chart 1) following withdrawal, we preferred to repeat its administration until a more lasting effect was procured. Being

aware of the toxic effect of the drug on the heart, we were on the lookout for cardiac signs, and rather concerned because of the relatively large size of the total dose and its well-known cumulative effect. Perusal of the literature leads me to conclude that should another opportunity arise, I would control its use by periodic electrocardiograms.

With regard to the blood chemistry (see Table 1) the low total cholesterol and the abnormal ester to free ratio in the early period followed by a return to more normal figures is interesting. The normal phosphatase with a serum bilirubin of 18.7 at the outset and the gradual increase of the former as the latter decreased is also of interest. I am unable to offer a satisfactory explanation.

TABLE 1.—BLOOD CHEMISTRY DATA.

Date, 1941.	Plasma cholest.	Phosphatase.	Bilirubin.	A/G ration.	Ceph. test.	NPN, mg.
2/22		3.7	18.7	..	Neg.	
2/25	64 { F—42 C—24	2.3				
2/27		4.7				
3/1	..	5.7	12.5	A = 3.1 = 1.4 G = 2.2	Neg.	50
3/5			3.9			
3/7	146 { F—47 C—99	10.1				
3/24	150		0.9			
4/14	..	11.1	Tr.			

The white count was elevated to around 15,000 throughout the illness with a relatively high neutrophil count.

Summary. 1. Acute abdominal symptoms and signs associated with fever and leukocytosis were erroneously diagnosed as appendicitis.

2. Removal of a normal appendix was followed by jaundice, abdominal distention, tenderness over the liver and fluid in the right chest. A low serum phosphatase was associated with high serum bilirubin.

3. Amebæ were found in the stool.

4. Three courses of emetine administration were necessary to effect a cure of the amebic hepatitis.

AN ACUTE PERFORATED DUODENAL ULCER FOLLOWING METRAZOL THERAPY.

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THE rare occurrence of an acute perforated duodenal ulcer following 1 week after metrazol treatment merits some consideration beyond assuming that it is mere coincidence. Recently, Moore

and Friedman¹¹ reported 2 cases of ruptured duodenal ulcer in young adult males occurring 9 to 17 months respectively after metrazol injections. They suggested that although considerable time had elapsed since the metrazol treatment had been instituted, in view of the neurogenic theory of the origin of peptic ulcers, pathologic changes in the brain or a disturbance of the autonomic nervous system may have been sufficient to initiate the ulcers. DeBakey⁵ reviewed the subject in general of acute perforated gastro-duodenal ulceration and Vonderahe¹⁹ discussed the various theories dealing with the cause of peptic ulcers, particularly from the neurogenic viewpoint. Stender,¹⁸ Reitmann¹⁴ and Liebert and Weil⁹ studied the effect of metrazol on the nervous system. Roback and Miller¹⁵ found sub-arachnoid and intracranial hemorrhages following 9 injections of metrazol. Hassin⁷ found nerve cell changes in a patient who had metrazol injections preceded by insulin shock treatment. From studies on dogs and rabbits, Whitehead *et al.*²⁰ suggested that the pathogenesis of the brain lesions is due to the anoxemia resulting from the vascular spasm caused by the convulsions.

Case History. A female, aged 52, entered this hospital with the complaint of severe abdominal pain. There was generalized boardlike rigidity of the abdomen and tenderness on palpation. The patient had first noticed abdominal pain 30 hours before entrance to the hospital. The respirations were rapid and shallow, the pulse very rapid, weak and irregular. The systolic blood pressure was 60, the temperature 104° F. An indirect blood transfusion was given, intravenous fluids and 4 gm. of sodium sulfapyridine in 500 cc. of distilled water. The Levine tube with continuous suction was used. The patient expired 6½ hours after admission. Five days before entering the hospital, she received an injection of metrazol for involutional melancholia which resulted in typical convulsive seizures. One or two injections had been given previously. There was no history or evidence of trauma to the epigastric region.

Autopsy findings (abdominal incision only): The abdomen contained considerable gas; the peritoneum was dull, purple-gray mottled with fibrinous deposits and contained about 500 cc. of dark brown fluid. There was a punched-out perforation (7 by 6 mm.) in the anterior surface of the first portion of the duodenum 1 cm. from the pylorus. Its edges were soft and brown stomach contents could be expressed. The anterior surface of the stomach was covered with a fibrinous exudate. The lesser peritoneal sac contained no fluid and the surfaces were smooth. The loops of small intestine were heavy and contained large amounts of fluid. In several areas, the serosa was covered by a fibrinous exudate.

Microscopic examination: The walls of the duodenal ulcer showed necrotic tissue along the edges of the ulcer, beneath which were small infiltrations of lymphocytes, mononuclear cells and neutrophils. No evidence of fibrosis was found (Van Gieson). The anatomic diagnosis was generalized fibrinopurulent peritonitis, acute perforated duodenal ulcer and fatty degeneration of the liver.

Discussion. The punched-out nature of the defect in the anterior wall of the duodenum, the lack of hemorrhage in the wall adjacent to the perforation, the absence of any evidence of direct injury to the epigastrium together with the absence of a history of a chronic

ulcer serves to eliminate a traumatic origin of the ulcer, except for the possibility of excessive flexion during the convulsion as a possible contributing factor. The thickened appearance of the anterior wall of the proximal 3 cm. of the duodenum was found to be due chiefly to large groups of Brunner's glands in the submucosa (Fig. 1). Comparison of the anterior wall of the first portion in the normal duodenums of other autopsies, together with the extensive studies of Feyrter⁶ and Robertson¹⁶ on the pathology of Brunner's glands, leads to the conclusion that the suspected hyperplasia came within the upper limits of normal. The possibility of abnormal pressure on the duodenal mucosa was considered because of the earlier contention of Scagliosi¹⁷ that duodenal ulcers may be caused by hyperplasia of Brunner's glands with subsequent pressure on the mucosa. However, this theory has not been substantiated by later investigators.



FIG. 1.—A sagittal view taken through the first part of the duodenum at a point 2 mm. from the right edge of the perforating ulcer of the anterior wall.

An attempt to explain the way in which metrazol could produce peptic ulceration necessitates consideration of vascular and neurogenic factors. Experimental work leading to the production of peptic ulcers strongly suggests that the main underlying factor is a local circulatory disturbance. Boles, Riggs and Griffiths³ and Boles and Riggs² concluded that focal gastric ulcers were due to focal manifestations of a generalized circulatory insufficiency. Also the work of Reeves,¹³ Wilkie²¹ and the more recent investigations of Wilmer²² on the blood supply of the first part of the duodenum give some anatomic basis for explaining the localization of ulcer lesions in the pyloric region of the gastro-intestinal tract. In the studies of Berg¹ and Nedzel,¹² on the experimental production of peptic

ulcers by means of pitressin, anoxemia is produced not only by direct action on the small blood-vessels but by a compression of the larger blood-vessels by muscular contractions of the walls of the stomach and duodenum.

The action of large doses of metrazol on the vascular system according to Hauray and Gruber⁸ is similar to the effect of adrenalin. They concluded from experimental studies that two effects on the vascular system may be obtained, depending on the size of the dose of metrazol: one a central action causing splanchnic constriction, and the other a peripheral effect causing splanchnic dilatation. Messinger and Moros¹⁰ have noted that patients with hypersensitivity of the sympathetic nervous system may exhibit symptoms of hyperadrenalinemia.

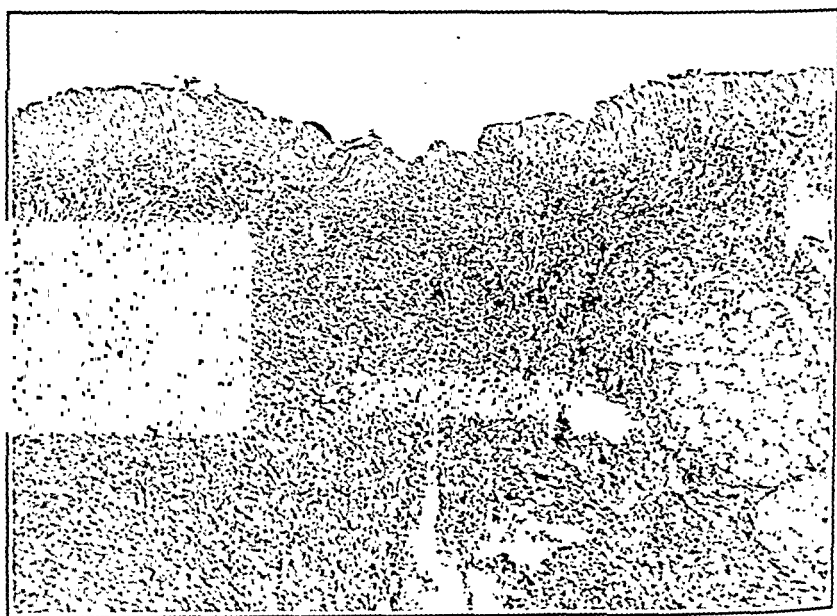


FIG. 2.—Section through the wall of the perforation, showing the distinct muscular coats and the narrow necrotic zone lining the defect. No fibrosis of a chronic ulcer is present. ($\times 40$.)

Certain neurogenic impulses can have profound effects on the terminal vascular system of the gastro-intestinal tract (Boles and Riggs²). This may appear after injury or stimulation of the brain, particularly of the hypothalamic regions. The stimulation of the vegetative centers may cause peripheral stasis or vasoconstriction through an imbalance of the sympathetic and parasympathetic nervous systems. This concept is essentially that used by Cushing⁴ to explain the pathogenesis of peptic ulcer. He concluded that abnormal vagal impulses could lead to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity particularly in the pyloric region,

causing spasmodic contractions of the musculature and possibly spasms of the terminal blood-vessels, leading to a devitalized area which may be then acted upon by the gastric juice.

Summary. The occurrence of an acute, perforated duodenal ulcer following soon after metrazol therapy is reported. The theories considering the possible relationship of the effect of metrazol on the nervous system and a "neurogenic" ulcer are briefly discussed. In view of the rarity of this type of complication following metrazol injections, however, the possibility of coincidence must be considered.

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A DIET CALCULATOR FOR SIMPLIFYING DIET PRESCRIPTION IN DIABETES MELLITUS.

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MANY of the significant advances in the science of nutrition have not been applied in the treatment of disease. This discrepancy between principle and practice may be due in part to the fact that many physicians have not been trained adequately in practical dietetics and in part to the fact that the writing of diet prescriptions remains a time-consuming procedure. As a result, it is a common practice to use a few favorite stock diets instead of giving patients individual dietary attention. This criticism may be directed particularly toward the dietary management of diabetes mellitus or

other conditions in which it is desirable to regulate accurately the caloric value of the diet as well as the content of carbohydrate, protein and fat.

The Diet Calculator. In an attempt to simplify this problem the essential information used in the dietary treatment of diabetes mellitus has been assembled on a circular chart called a Diet Calculator.* By manipulating the movable parts of this instrument one may select the desired therapeutic diet to meet the needs of a particular case.

The device, as illustrated in Figure 1 consists of three concentric disks, the two outer disks form the front and back dial faces and rotate upon a slightly larger inner disk. One hundred diets are listed. The various details of a single diet may be read through the windows of the dial face as its pointer is directed toward a given sector on the periphery. Figure 1 illustrates the front view; the back view is similar except that the diets possess higher caloric values.

Use of Calculator. The number of calories required for a given patient may be determined by reference to the tables upon the face of the Calculator. After choosing the level of calories and selecting that specific division on the periphery of the Calculator, one then selects a diet within that range of calories by rotating the pointer of the dial face to the desired amount of available glucose† listed in the most peripheral window, or if preferred, to the content of carbohydrate, protein and fat named in the second window. The characteristics of the diet in terms of basic foods may then be read through the remaining windows, in which are listed the total food required for the day and the amounts of food for each of the three daily meals.

The following basic food groups are used: eggs, bacon, milk, 10% fruit or vegetable, bread, 20% cream, and butter. For convenience the principal source of protein is expressed in terms of eggs, other protein-containing foods which may be substituted for eggs are tabulated upon the back face of the instrument. The bulk of the diet may be regulated by substituting 5%, 15%, or 20% fruits and vegetables for amounts of 10% fruits and vegetables. The quantities of the various foods are such as to be readily convertible to measure if weighing of the diet by means of a gram scale is not desired. The classification of fruits and vegetables according to carbohydrate content in terms of 100 gm. portions with the equivalent in household measures is tabulated on the back dial face.

In these diets the morning meal contains $\frac{1}{3}$ and each of the two remaining meals $\frac{2}{3}$ of the total daily available glucose. By means of a simple adjustment as described on the front dial of the Calculator, it is possible to secure either an equal division of the available glucose among the three daily meals ($\frac{1}{3}-\frac{1}{3}-\frac{1}{3}$) or to allow for a bedtime feeding ($\frac{1}{3}-\frac{1}{3}-\frac{1}{3}-\frac{1}{15}$).

* Published by E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

† The available glucose is derived from the metabolism of 100% of the carbohydrate, 50% of the protein and 5% of the fat. (Newburgh and MacKinnon, *The Practice of Dietetics*, New York, The Macmillan Company, 1934.)

AVAILABLE GLUCOSE IN GRAMS

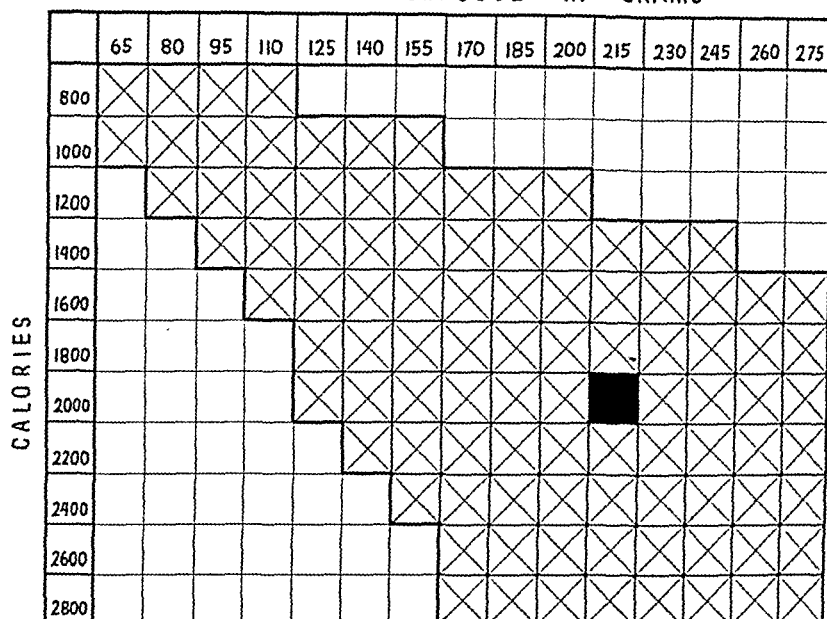


FIG. 2.—The crossed squares represent the combinations of calories and available glucose in the 100 related diets. The inked square designates the prescription from which successive isocaloric diets and successive diets of constant available glucose content were prepared.

CALORIES	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
AVAILABLE GLUCOSE GRAMS	125	140	155	170	185	200	215	230	245	260	275	
TOTAL FOOD FOR DAY												
EGGS	7	7	7	7	7	7	7	7	7	7	7	7
BACON	20	20	20	-	-	-	-	-	-	-	-	-
MILK	24.0	24.0	24.0	36.0	36.0	36.0	60.0	60.0	60.0	60.0	60.0	60.0
10% FRUIT	18.0	29.0	35.0	32.0	34.0	30.0	34.0	36.0	42.0	45.0	47.0	

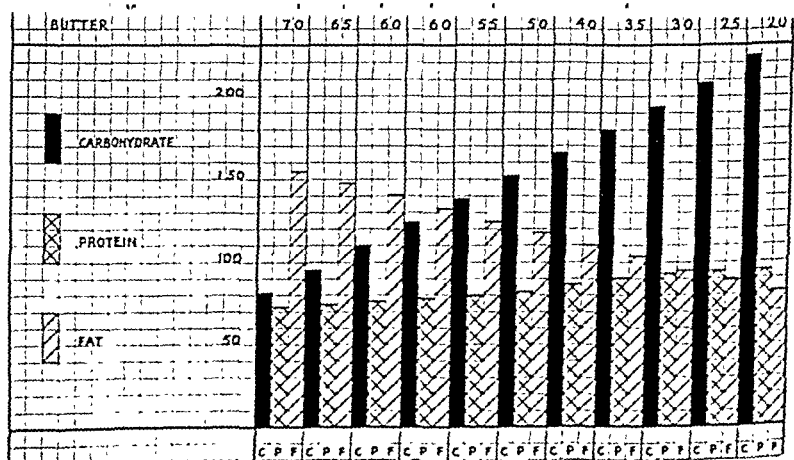


FIG. 3.—Composition in terms of food groups, carbohydrate, protein, and fat of the isocaloric diets of 2000 calories and a varying content of available glucose.

from 125 to 275 gm. In reading this sample series from left to right one should note the steplike increases in carbohydrate and the decreases in fat existing between the individual diets, also the graded variations in the constituent food groups. It is to be observed that the prescriptions toward the left of the series are of relatively low carbohydrate and high fat value, those toward the right of relatively high carbohydrate and low fat value, whereas the diets mid-way between these two extremes possess a ratio of carbohydrate to fat of approximately 1 to 1.

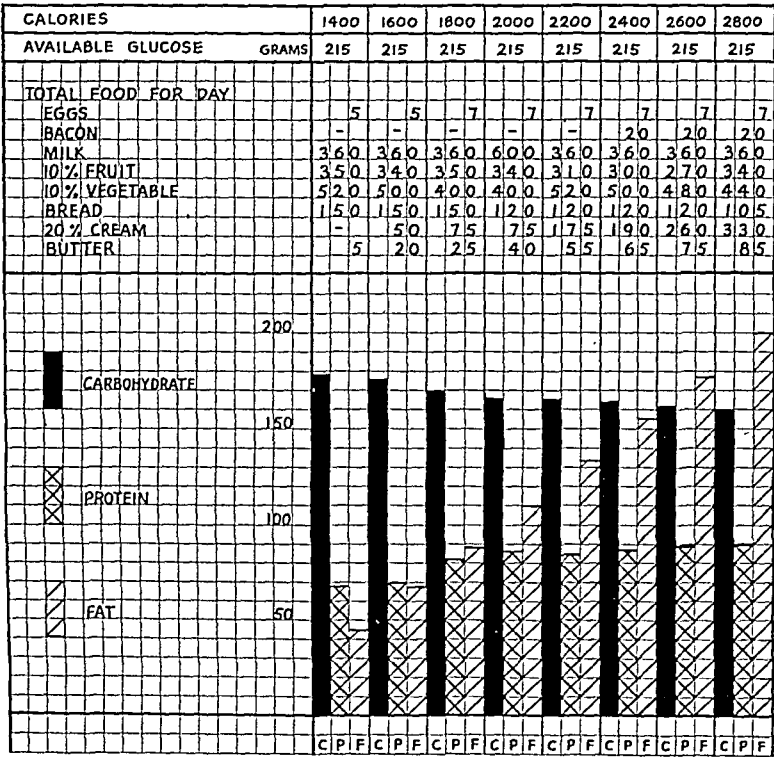


FIG. 4.—Composition in terms of food groups, carbohydrate, protein and fat of diets containing 215 gm. available glucose and a varying content of calories.

When the squares of Figure 1 are viewed in vertical columns, the individual diets have a constant level of available glucose but vary by units of 200 calories. Figure 4 illustrates the composition of the diets of a sample vertical series, namely those containing 215 gm. available glucose as the calories are carried through the range from 1400 to 2800. As in the previous example, one may observe the variations between the individual diets in terms of carbohydrate, protein, and fat as well as in the constituent food groups.

Mathematical Construction of Diets. The preparation of this series of 100 interrelated diets may now be explained. The diet of 2000 calories and 215 gm. available glucose (see inked square in Figure 2) served as the starting point. Other diets of 2000 calories

containing progressively less available glucose (*i. e.*, 200, 185, 170, etc. gm.) were constructed by making repeated subtractions in terms of foods rich in carbohydrates and repeated additions in terms of foods high in fat value. A formula was prepared listing the increments or decrements in terms of the basic food groups as well as the resulting change in the values of carbohydrate, protein and fat which occurred in a reduction of 15 gm. available glucose (*i. e.*, moving one square to the left in Figure 2). The successive isocaloric

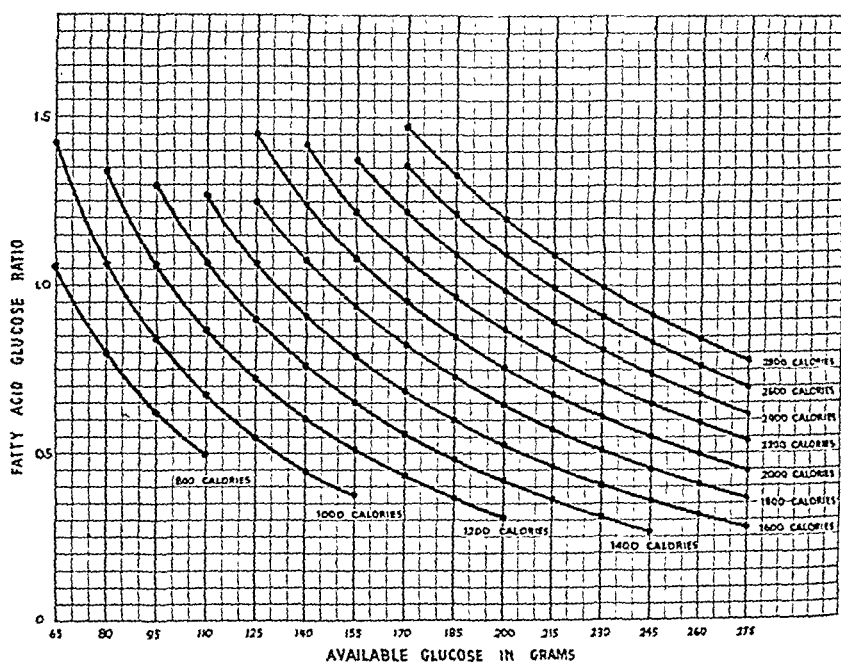


FIG. 5.—The fatty acid glucose ratios of the standard diets of the Calculator. Interesting from the mathematical standpoint is the fact that the individual points making up the curves of this figure may be on semicubical parabolas according to the equation:

$$\frac{\text{Fatty acid}}{\text{Glucose}} = \frac{1.155 \text{ calories} - 390}{(\text{Available glucose})^{3/2}}$$

(This equation was contributed by Dr. John Bugher.)

diets of decreasing available glucose content were prepared in the same manner. Conversely, the formula with opposite signs was used in constructing adjacent isocaloric diets of increasing available glucose content (*i. e.*, moving square by square to the right in Figure 2).

The successive diets in the vertical series of 215 gm. available glucose and varying calories (see Figure 2) were constructed in a similar mathematical fashion, again starting with the initial diet of 2000 calories and 215 gm. of available glucose (see inked space).

The same formula was not used in constructing each successive diet of an entire horizontal or vertical series. At intervals within each series the formula was changed in order to regulate the bulk of the diet and to keep the prescriptions well balanced.

The fatty acid glucose ratio of each diet is plotted in Figure 5. Connecting the plotted points for each group of isocaloric diets results in a series of arcs the curvature of which decreases as the caloric values increase. It will be noted that in no instance does the ratio exceed 1.5.

The use of this mathematical approach results in a series of 100 closely related therapeutic diets. The constant and gradual change occurring between individual isocaloric prescriptions is a significant feature. Under certain circumstances it is desirable to change a diabetic diet by small and repeated increments or decrements of carbohydrate. These prescriptions are constructed to allow for such manipulation with the least possible alteration in the diet's basic structure yet maintaining the calories at a constant level.

Accompanying the Calculator is a booklet of instructions which explains in detail how the instrument is used. Included in the booklet are substitution tables which may be used in case one wishes to convert the standard diet prescriptions of the Calculator to diets of higher protein content. There is also provision for the addition of milk to children's diets.

By reference to other tables the caloric or available glucose content of a given diet prescription may be increased or decreased. These tables are useful in cases where the standard diets of the Calculator have been altered in terms of the constituent basic foods. An alteration, such as the addition of milk to the diet of a child, may be retained as the energy value of the prescription is changed by units of 200 calories or the available glucose altered by 15 gm. In each case the resulting value of carbohydrate, protein and fat is tabulated.

No attempt is made to outline procedure in the dietary therapy of diabetes mellitus. This material is presented with the aim of supplying in a simple and usable form the essential dietary information applicable to the treatment of diabetes. Depending upon the needs of the particular patient or upon the point of view of the physician, one may select adequate diets of varying energy content relatively high or low in carbohydrate, protein or fat.

Summary. A Diet Calculator listing the details of 100 therapeutic diets and providing for alterations in these prescriptions to meet the requirements of individuals with diabetes mellitus is described.

The mathematical approach in constructing this series of inter-related diets is explained.

BOOK REVIEWS AND NOTICES

ALLERGY IN CLINICAL PRACTICE. By Staff-members of the Cleveland Clinic. Under the Direction of RUSSELL L. HADEN, M.D., F.A.C.P., Chief of the Medical Division; Edited by J. WARRICK THOMAS, M.D., F.A.C.P., Chief of the Section on Allergy. Pp. 354; 92 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$5.00.

THE concept responsible for this volume, to write for the general practitioner a text on allergy with a minimum of theory and technique and with a maximum of the practical as set forth in numerous case reports, is most laudable, but the result leaves much to be desired. After a very inadequate introductory chapter on the "Approach to the Problem of an Allergic Patient" (in which pruritis is referred to as a lesion), there follow chapters on asthma, hay fever, perennial nasal allergy, allergic bronchitis, bronchiectasis, the cutaneous allergies, gastro-intestinal allergy, the ocular manifestations of allergy, migraine, endocrine considerations in the allergic patient, uncommon manifestations of allergy. Only the chapters on the cutaneous manifestations of allergy deserve high praise. By contrast the chapter on asthma is sketchy and incomplete. The discussion of gastro-intestinal allergy is very inadequate. The chapter on endocrine considerations is not pertinent and only beclouds the issue. Urinary tract allergy is dismissed with 3 case reports. Very few of even the most enthusiastic allergists would subscribe to the view that *all* hay fever patients should be thoroughly tested to foods as well as inhalants. The book is not recommended.

R. K.

L'ÉTAT PRÉ-CANCÉREUX. Signification Biologique. By J. M. MONTPELLIER, Professeur of Pathological Anatomy, School of Medicine, University of Algiers, North Africa. Pp. 268; with numerous plates. Algiers: Jules Carbonel, 1941. Price about \$2.00 (52 francs French).

THIS book, having as its purpose the study of the biologic concept of the precancerous state and the question of suitable cancer prophylaxis, contains much interesting information. Up to the present day the concept of the precancerous state has always been a subject for much controversy. While many cancerologists are of the opinion that the precancerous state is bound to manifest itself as cancer sooner or later, others regard it as one which may or may not manifest a tumor later on. According to still other scientists, a lesion is either cancerous or non-cancerous; and, from the biologic, clinical, and histologic standpoints, it is impossible to diagnose the "precancerous state."

The author, in spite of the complexity of the problem, attacks it very courageously, and gives us a very interesting and instructive book.

Book I deals with the precancerous state in humans. Its characteristics are a local process accompanied by a general process. To quote the author: "When we observe the initial stages of cancer, we notice a phenomenon which is constant—the malignant tumor does not appear haphazardly, at any part of the body, or suddenly even. Before the appearance of a cancer, there are always local premonitory signs. This premonitory local state is always present in human and animal cancer cases before the appearance of the tumor. Thus, there is no cancer without a previous local precancerous state." In many cases, these precancerous states may regress and disappear entirely before a cancer has appeared. This phenomenon is noticed both during the development of a spontaneous cancer and during an experi-

mentally induced cancer. The fact that a precancerous state may disappear or develop into cancer itself in no way affects the biologic significance and importance of the precancerous problem.

Histologically, a precancerous state is a process of cellular and tissue change ("remaniement"), during which regressive and progressive phenomena are noticed. But what is striking in this connection is not so much the regression and the progression of tissue—the static state—but the dynamic state of the tissue. That is to say, an exaggerated and disorderly generative cell-action.

The author goes on to describe these local precancerous states—mild tumors, embryonic and organic malformations, scars, chronic irritations, intoxications and so on.

This book also deals with the precancerous states in comparative pathology, such as spontaneous and induced cancer in animals and plants. From the biologic point of view, all cancers, human or animal, induced or spontaneous, are always preceded by initial local lesions which are precancerous.

Book 2 deals with the biologic significance of the precancerous state. Precancerous states are of many different kinds and often give the clue to the cancer itself. No cancer appears without having first been "announced" by a local precancerous state. In this part of his book, the author gives clinical, histologic and chemical descriptions of these various states.

This part of the book also treats of the "cancerous terrain." The author concludes that it is logical to accept the existence of a general precancerous state, in certain patients. This general "precancerosis" is regarded as a specific receptivity of the body to cancerization. Thus, local conditions being the same in both cases, the patient with no receptivity does not develop cancer, while the other patient (who is receptive) does. But we must admit that on such speculative ground, investigation must be controlled with a special caution. For this idea of the precancerous state is important in all present-day practical cancerology. That is why this book should be read, not only by the cancerologist, but by physicians generally.

Book 3 deals especially with cancer prophylaxis. The author formulates numerous methods which may be used to: *a*, combat the transformation of a precancerous state into cancer itself; *b*, eliminate the formation of a precancerous state. These methods include hygienic measures designed to protect the skin, the mucosa, and the internal organs against local precancerous states. By general hygiene, such as special diet, the elimination of certain dangerous cancerogenic substances, such as drugs, certain food-stuffs, arsenic, folliculin, etc., the formation of cancer can be avoided. A special hygiene for the nervous system must also be used in cancer prophylaxis. As soon as a slight alkalosis of the blood, or a surplus of cholesterol, is observed, measures must be taken to eliminate these conditions. Chronic infection and intoxication must be avoided.

The author also deals with the question of hormones and precancer, professional diseases, and the counter-measures to be employed, the social and medical services which should function in each country, and a special cancerologic training for the medical body.

This is a book which should find a place in every doctor's library.

J. S.

SINUS. By RUSSELL CLARK GROVE, M.D., Assistant Otolaryngologist, and Chief Otolaryngologist of Allergy Clinic, Roosevelt Hospital. Pp. 188; 16 illustrations. New York: Alfred A. Knopf, 1941. Price, \$2.00.

WRITTEN for the layman, who unfortunately has as a rule a large store of misinformation on "sinus," this book presents a discussion of the anatomy and physiology of the paranasal sinuses, the causes and types of sinus

disease, the symptoms, diagnosis and complications of sinusitis, and the rationale of the medical and surgical treatment of these conditions. While in places the going may be a bit heavy, the intelligent layman will find the book both useful and instructive.

R. K.

THE ECLIPSE OF A MIND. (Autobiography with a Preface by an "Anonymous Attending Physician.") By ALONZO GRAVES. Pp. 722. New York: The Medical Journal Press.

This is a hard book to review. It is unique in presenting a patient's account of manic-depressive attacks side by side with very good hospital records. The patient's sex life is given in voluminous detail. The chapter on heredity and environment is admirable as is the author's detached and scientific discussion of the "bored and kindly custodial treatment of human livestock." His discussion of the origin of mania in himself is full of good suggestions and is well thought out. Not the least surprising thing in this unusual book is the author's disappearance into Russia.

It will be of great interest to psychiatrists and also to workers in fields related to psychiatry. Because of the unusual character of this book, attitudes toward it will depend much on the background of the reader.

E. B.

SYMPTOM DIAGNOSIS. Regional and General. By WALLACE MASON YATER, A.B., M.D., M.S. (in Med.), F.A.C.P., Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Physician in Chief, Georgetown University Hospital and Gallinger Municipal Hospital, Washington, D.C., Formerly Fellow in Medicine, The Mayo Foundation. (Originally written by the Late WILFRED M. BARTON, A.M., M.D., F.A.C.P., and WALLACE M. YATER, A.B., M.D., M.S., F.A.C.P.) Fourth edition. Pp. 900. New York: D. Appleton-Century Company, 1942.

A USEFUL and convenient book for quick reference and help in diagnosis. It is concise, yet adequate. The material is well arranged and there are numerous classifying tables. The work, which justly merits its fourth edition, is highly recommended.

R. K.

THE MODERN TREATMENT OF SYPHILIS. By JOSEPH EARLE MOORE, M.D., with the collaboration of J. E. KEMP, M.D., HARRY EAGLE, M.D., PAUL PADGET, M.D., MARY STEWART GOODWIN, M.D. Pp. 674. Second edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$7.00.

COMING as it does from an originator of and spokesman for many of the most significant contributions, clinical and experimental to the syphilology of today, this new edition must be read by every serious student of medicine in one or another chapter of its many-sided presentations. It achieves with success the compromise between the encyclopedic authority and the practical utility of the desk volume. Part of this excellent effect is secured by hewing close to the line of the major contributions of the Johns Hopkins group, which are of a range and depth sufficient to reflect and voice the entire field. Certain of the chapters, as on syphilis of the eye and of the nervous system, are monographs embodying unrivaled experience, and will be repeatedly referred to by clinicians in one or another "tight spot." Similarly there are modestly tucked away in other presentations (as in early syphilis) gems of original contribution whose luster can best be appreciated by the expert who has watched the progress of thought in this field.

over a period of years, and knows that they represent pivotal points that determined the course of future thought and procedure.

The defects of the work, as the reviewers see them, are of much less significance, and are perhaps inevitable by-products of a group mode of approach, carried to its conclusion. The work was directed by one of the most brilliant, incisive, positive, and critical minds in the field. It is to be expected and indeed hoped that it will contain *obiter dicta*, *ipse dixit*, and *ex cathedra* statements, not always on adequately examined premises. It does. It requires no use of the vulgar device of illustration (p. 175) to make a sensitive reader read page after page of flat print indulging now and again in the excellent exercise of grinding his teeth and bounding from his chair. All this is for the best, and stimulating both for the cerebral vertex and the suprarenal medulla. If the authorship can carry the pace, the reader should, and he will; but not without creaks over the corduroy. There is an apparent disposition to cite outside views for the purpose of demolishing them, sometimes with needless acerbity, or to interpose the negative on insufficient or admittedly no evidence. There are outright misstatements of others' views quoted from obsolete citation (*cf.* the resistance building *vs.* the spirocheticidal mechanism in bismuth action), apparently to act as foils for the authors' more recent contributions. The strong group flavor sometimes becomes overwhelming like the otherwise laudable and delectable odor of allyl sulphide which in sufficient concentration can provoke tears. The best description of the ninth day erythema (stated to be a neglected topic, though adequately described in at least two American and many European sources) is by a Johns Hopkins author not yet in print at the time of this book's citation. This disposition to beat the starting gun confers merely an added piquancy. But the bibliography thus drawn must be emphatically described as inadequate and a bit deceptive—especially since statements are not tagged to their bibliographic citations in many cases, so that a reader cannot check or judge strictures and evaluations from their context. There are occasional indications, as in the interpretations of non-specific effects of treatment, that the writing of a text on syphilis from the viewpoint and equipment of an internist may have its shortcomings, like writing from that of a dermatologist or other -ologist.

But all this is minor animadversion and really praises the work as human, as well as stimulative, informative, authoritative. The best and the most final comment on Moore on Treatment is this: when the expert of the future and the historian of the past prepare to write on the management of syphilis they will have to read Moore, word by word, or miss the essence of the subject.

J. S. N. I.

TREATMENT OF THE PATIENT PAST FIFTY. By ERNEST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City; Chairman, Committee on Chronic Illness, Welfare Council of New York City; Assistant Clinical Professor of Medicine, Columbia University. Pp. 324; 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, \$4.00.

THE past 50 years have witnessed a steady increase in the proportion which the elderly comprise in our population. It has been estimated that, if present trends continue, by 1980 nearly 15% of the American people will be past the age of 65. The present text deals with problems of prophylaxis, diagnosis and treatment of disease in those past 50. From the standpoint of the various organic diseases, which are systematically discussed, the material is well handled. More might have been said about functional disorders and the psychic and medico-social problems so common among those of advanced years. Especially the young physician will find much that is helpful in this book.

R. K.

ROENTGEN TREATMENT OF INFECTIONS. By JAMES F. KELLY, M.D., F.A.C.R., Professor and Director of the Department of Radiology, Creighton University School of Medicine; Attending Radiologist, Creighton Memorial, St. Joseph's, St. Catherine's and Douglas County Hospitals, Omaha, and Mercy Hospital, Council Bluffs: With the Collaboration of D. ARNOLD DOWELL, M.D., Assistant Professor of Radiology, Creighton University School of Medicine, etc. Pp. 432; 122 illustrations. Chicago: The Year Book Publishers, Inc., 1942. Price, \$6.00.

THIS is a carefully prepared textbook with a good index and extensive bibliography. It includes a review of all cases of gas gangrene, treated by Roentgen ray, in this country, that have come to the authors' attention.

The first two chapters of the book contain a brief discussion of Roentgen ray physics and general considerations of Roentgen ray therapy in infections with a history of the development of the mobile therapy machine. The main portion of the book deals with the Roentgen ray treatment of gas gangrene and acute peritonitis. The authors are pioneers in this field and have drawn on their experiences in the management of these serious infections over more than 10 years. They produce convincing proof that in their hands early Roentgen ray treatment for gas gangrene and acute peritonitis is the method of choice. In both gas gangrene and peritonitis, Roentgen ray treatment should be given in small doses every 8 to 12 hours for the first few days until the toxemia of the disease has disappeared. Under this régime, early amputation and the use of serum is superfluous and may actually do harm. The authors believe that the use of sulfanilamide with Roentgen ray treatment is contraindicated, and that Roentgen ray alone has proven more beneficial than sulfanilamide alone, in the rapidly spreading anaërobic infections.

The last three chapters deal with the Roentgen ray treatment of superficial infections, parotitis, and other conditions, also, the writers believe that Roentgen ray therapy may be a life-saving procedure.

There is no doubt that the authors have made a very important contribution to the practice of medicine through years of patient investigation in the field of treatment of infection, particularly gas gangrene, by Roentgen rays. It must be said, however, that the conversational style of this book and its frequent unnecessary repetition detract somewhat from the valuable material presented. All the essential points could be covered in a much smaller number of pages, and the result would be made easier to read.

R. B.

SURGERY OF THE AMBULATORY PATIENT. By L. KRAEER FERGUSON, A.B., M.D., F.A.C.S., Lieut.-Commander, Medical Corps, United States Naval Reserve; Assistant Professor of Surgery, University of Pennsylvania; Assistant Surgeon, Hospital of the University of Pennsylvania; Surgeon, Philadelphia General Hospital and Doctors Hospital; Consulting Surgeon, Frankford Hospital; Chief of the Surgical Out-patient Department, Hospital of the University of Pennsylvania; Chief of the Proctologic Clinic, Hospital of the University of Pennsylvania and Philadelphia General Hospital. With a Section on Fractures by LOUIS KAPLAN, A.B., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania; Associate in Surgery, Mt. Sinai Hospital; in charge of the fracture division of the Surgical Out-patient Department, Hospital of the University of Pennsylvania. Pp. 923, 645 illustrations. Philadelphia: J. B. Lippincott Company, 1942. Price, \$10.50.

THE average surgeon is apt to overlook the fact that actually the greatest number of surgical lesions are the so-called minor ones, that is, they do not require hospitalization of the patient. These lesions are, as a rule, treated by the general practitioner or by the younger surgeon. They do, neverthe-

less, require skill and judgment in therapy for disfiguring and even disabling results may follow careless treatment.

Doctor Ferguson has had many years of experience as head of an active surgical out-patient department. This volume is the result of his thoughtful approach to the surgical problems he has had to meet. It is a comprehensive, clear exposition of the surgical therapy he has found to be most effective and it can be fully recommended to every industrial or general surgeon.

The only criticism that might be offered is that a number of procedures are included which in the hands of Doctor Ferguson, who is an experienced general surgeon, might be safely done in the ambulatory patient, for example, the excision of a thyroglossal sinus, but which should not be done by a less skillful surgeon under these circumstances. I believe in the next edition of this book it would be well to include a few words of caution after certain of the more extensive procedures.

The illustrations are clear and numerous and the book is well arranged and well printed.

I. R.

THE LYMPHATIC SYSTEM: ITS PART IN REGULATING COMPOSITION AND VOLUME OF TISSUE FLUID. LANE MEDICAL LECTURES. By CECIL K. DRINKER, Professor of Physiology and Dean of the School of Public Health, Harvard University. Pp. 101; 29 illustrations. Stanford University Publications, University Series. Medical Sciences, Vol. IV, No. 2, Stanford University, California, Stanford University Press, 1942. Price; bound \$2.25; in paper, \$1.50.

THE author's Preface explaining why this shorter book so soon follows his longer one on the same subject, aptly likens the essay to "a cruise in a ship built of experiments and ideas." He here develops the reasons why mammals have a lymphatic system, and why it has slowly developed into an important physiological entity complementing the blood circulation. The student of this short book will inevitably profit by the stimulating presentation of the evolution and function of the lymphatic apparatus; he may be even more stimulated and benefited by the author's persistent emphasis, in his well known picturesque and vigorous style, on the dynamic point of view and on the need for ideas and on their harmfulness unless converted through experiment into fact.

The twenty-eighth series of Lane Medical Lectures will stand high among its distinguished predecessors.

E. K.

THE ELECTRON MICROSCOPE. By E. F. BURTON, Head of the Department of Physics and Director of the McLennan Laboratory, University of Toronto, and W. H. KOHL, Development Engineer, Rogers Radio Tubes Limited, Toronto. Pp. 233; 110 illustrations. New York: Reinhold Publishing Corporation, 1942. Price, \$3.85.

KNOWLEDGE of form and structure has regularly and almost necessarily preceded knowledge of function—first knowledge of what might be seen with the naked eye, then of greater detail as supplemented by the magnifying powers of the microscope and telescope. It was not until a century ago that technical improvement of the compound microscope, especially with good achromatic lenses, permitted the accurate knowledge of plant and animal tissues in health and disease that revolutionized the biological sciences. In simple but accurate language, the authors explain the physical reasons for the limitations of the resolving and magnifying powers of the ordinary light microscope and of the slightly more powerful, "ultramicroscope." Thus the highest practical magnifications, 1800 to 2500, were capable of revealing the smallest bacteria, but not the filtrable viruses, even the largest molecules and so on.

DeBroglie's development of the theory of the dual nature of the electron (1923) opened the way to a new field of study, Electron Optics, and this in turn to the production of Electron microscopes, both electrostatic and magnetic, that permit of useful magnifications 20 to 50 times greater than had been previously possible. Already, in the medical field, for instance, it has become possible to photograph the viruses (Cp. on page 218, smallpox viruses, $\times 113,400$). Important new discoveries are being announced so rapidly that Koch's early days of bacteriology are recalled when it was necessary merely to shake the tree and new bacteria fell like ripe apples.

Such is the great story told by this little book, for the most part in simple language, together with the necessary underlying physics. The future usefulness of the method for many diverse fields of scientific investigations is indeed hard to exaggerate. Let us hope that the good start made on this Continent toward its practical applications may continue in spite of world conditions and even be a source of practical help to the United Nations in their vital struggle.

Those who know this field better than I tell me that this is a sound, reliable, well written book that fills an immediate need. One is surprised, however, at the kind of paper and screen used for the illustration of such difficult and highly magnified material.

E. K.

MODERN BREAD FROM THE VIEWPOINT OF NUTRITION. By HENRY C. SHERMAN and CONSTANCE S. PEARSON, Columbia University. Pp. 118. New York: The Macmillan Company, 1942. Price, \$1.75.

MODERN bread is a scientific attainment. Many advances in the growing of better wheat, in the milling of flour, improving its keeping qualities, and so on, have been made. But while the fine white bread of today retains its energy value and is more palatable and more generally digestible than the coarse dark bread of earlier times, it has suffered the loss of certain of its most valuable proteins, minerals and vitamins. The problem of the nutritionist is to suggest ways for the enrichment of flour or of bread so as to restore these lost constituents.

This book, from one of our leading laboratories of nutrition, has reviewed the whole question, and indicates the many possible ways by which a bread may be produced that, while furnishing as high as 50% of the total calories, will at the same time provide adequate calcium, iron, essential amino acids, and at least two of the important B vitamins, thiamin and nicotinic acid.

An excellent bibliography is appended, and a subject index.

E. W.

LANGUAGE IN ACTION. A Guide to Accurate Thinking. By S. I. HAYAKAWA, Assistant Professor of English, Illinois Institute of Technology. Pp. 245. New York: Harcourt, Brace & Co., 1941. Price, \$2.00.

AND

SCIENCE AND SANITY. An Introduction to Non-Aristotelian Systems and General Semantics. By ALFRED KORZYBSKI, Author, *Manhood of Humanity*, Director, Institute of General Semantics. Pp. 798. Illustrated. Second Edition. Chicago: The International Non-Aristotelian Library Publishing Company, 1941. Price, \$6.00.

To the many of us who have only in the past year or so become aware of Semantics as an important mental discipline it will be a surprise to learn that the first edition of "Science and Sanity," the key to the scriptures of this discipline, appeared in 1933; that there have been two International Congresses on the subject, 1935 and 1941; and that an Institute of General

Semantics has flourished in Chicago for the past 4 years. From the 34 page booklet of application and criticisms that accompanies Korzybski's second edition we further learn that many really eminent thinkers—philosophers, mathematicians, biologists, physicians, psychiatrists, lawyers, educators, industrialists—warmly endorse the fundamental importance of the concept for all branches of human thought.

Obviously it behooves us to know more about this. On page 19, we learn that the term "semantic" is derived from the Greek *semantikos* (significant) and was introduced into literature by Michel Bréal in his "Essai de Sémantique." Bréal was a French philologist (b. 1832) whose essay (1897) was concerned with the term in relations to *sema* (a sign or symbol, as in semaphore). When one seeks for further definitions, however, one finds that the author, a Polish Count, mathematician, and engineer, plunges quickly into higher mathematics, non-elementalistic structures, relativity, infinity, non-Aristotelian and "extensional" (*vs.* "intensional") concepts, and similar abstruse abstractions. Stimulus to persevere in this heavy going is not found by the physician in such statements as "Disturbances of the semantic reactions in connection with faulty education and ignorance must be considered . . . as sub-microscopic colloidal lesions." Nor is confidence engendered by the incompleteness of many of the references gathered mostly toward the end of the book.

One turns, therefore, with relief to Hayakawa's "Language in Action," an avowed attempt to interpret and popularize this new science of symbolism and especially to evaluate the meaning of words and to illustrate the influence of language on thought. Every thoughtful student or teacher of a subject who attempts to be accurate in thought and expression, soon comes to realize how many unnecessary misconceptions and misunderstandings obstruct progress through the use of ambiguous or misleading words or through substituting the abstract word for the concrete reality, the theory for the fact. These he will find adequately and entertainingly explained in the smaller book, together with other semantic pitfalls, such as the "loaded" ("snarl" or "purr") word, the "one-word-one-meaning" fallacy, the "two-valued orientation" (*e. g.*, that a question can have only two sides, as in "Have you stopped beating your wife?"), affective connotations and communications, dictionary limitations, and so on. If you are really concerned in making yourself understood by the other fellow and in understanding what he means rather than merely what he says, this book will surely help you, and it will, in passing, give you a much more satisfying attitude toward language as language. What a different world it would be if in daily conversation, in the public press, and in learned assemblies, one could always understand what the other was trying to convey! And in a crazy world, groping about for a lost *modus vivendi*, would not an adequate knowledge of Semantics be an important factor in producing a workable peace?

We strongly recommend this little book, written by an American citizen who for many years has taught in the Illinois institution, and a few readers; we believe, will find even greater profit in following the advice of the author of "Science and Sanity" that his book "should be read at least twice and preferably oftener."

E. K.

PEDIATRIC GYNECOLOGY. By GOODRICH C. SCHAUFFLER, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School. Pp. 384; 66 illustrations. Chicago: The Year Book Publishers, 1942. Price, \$5.00.

A TEXTBOOK dealing with pelvic diseases in children and adolescent girls is a welcome addition to the more general texts in this field. In his small volume the author opens with a discussion of the psychologic management

of the patient. He outlines the various methods of investigation of the pelvic diseases of children, describes their treatment, and includes chapters on urologic conditions and diseases of the rectum. A final chapter deals with the medicolegal aspects of rape and allied subjects.

The author takes a sensible view of the various remedies which have been suggested in the field of the endocrine therapy. All of his subjects are well covered. Few references are given and these appear as footnotes. A more extensive bibliography and one condensed at the end of the volume, which would include full titles, would enhance the value of the book.

The publishers have made an attractive volume; the print is large and easily read. The 66 illustrations are well chosen and clear. The author is to be congratulated upon giving due credit to those who assisted him in the preparation of certain chapters—a courtesy frequently overlooked by authors. The Reviewer recommends the volume to everyone who is practising general medicine.

D. M.

THE HISTORY AND EVOLUTION OF SURGICAL INSTRUMENTS. By DR. C. J. S. THOMPSON (with a foreword by DR. CHAUNCEY D. LEAKE). Pp. 106; 115 illustrations. New York: Schuman's, 1942. Price, \$8.50.

The author is well known to readers of English medical history through his numerous entertaining and valuable works on various phases of the physician's and the apothecary's art. As Curator of the Royal College of Surgeons in Lincoln's Inn Fields, he fortunately had recently completed the present study, based largely on the collection in that Museum, before it was wiped out by Nazi vandalism. It is fortunate that we have at least this valuable substitute for the destroyed collection and its descriptions. Scalpels, saws, trephines, specula, forceps, lancets, tourniquets, trocars, operating tables—these are the kinds of instruments traced by Dr. Thompson from Egyptian and Grecian down to modern times. Excellent and necessary as are the many illustrations, one almost begrudges the space that they take to the exclusion of further information from this well-informed writer.

The book is unusually well-prepared and should be a valued possession of many more than surgeons and medical historians.

E. K.

RABIES. By LESLIE T. WEBSTER, M.D., The Rockefeller Institute for Medical Research, New York. Pp. 168, 2 illustrations, 22 tables. New York: The Macmillan Company, 1942. Price, \$1.75.

It is certain that control of communicable diseases demands enlightened community effort based upon complete understanding of responsibility. It is equally certain that ignorance combined with emotional factors have prevented the eradication of rabies. But with this book available there can be no excuse for ignorance on the part of veterinarians, public health officers or physicians. In it the author has set out briefly and concisely the available facts necessary for complete understanding of rabies, its diagnosis and control. The book is divided into three parts: 1, The diagnosis of rabies; 2, the prevention of rabies; and, 3, "Appendices," in which are quoted statutes on the disposal of rabid dogs, licensing dogs and disposal of unowned dogs, disposal of vicious dogs, and confining animals to prevent spread of rabies. In addition, tables on the immunizing potency of antirabies vaccines are included, and rabies antibodies and their relation to immunity are discussed briefly. There is an adequate bibliography and an index. Throughout the book "what to do and how to do it," when rabies is suspected in a community or when man or animals have been bitten by rabid dogs, is emphasized. The book may be recommended without reservation. The author is to be congratulated.

H. R.

NEW BOOKS.

Solving School Health Problems—The Astoria Demonstration Study. By DOROTHY B. NYSWANDER, Ph.D. The Commonwealth Fund, Publishers, New York: 1942. Pp. 377; several tables. Price, \$2.00.

A Short History of Nautical Medicine. By LOUIS H. RODDIS, M.D., Captain, Medical Corps, U. S. A. Published by Paul B. Hoeber, Inc., New York: 1942. Pp. 359; illustrations, 12. Price, \$3.00.

Acute Injuries of the Head. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Published by Williams & Wilkins Co., Baltimore: 1942. Pp. 288; illustrations, 124. Price, \$6.00.

Arthrodesis. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Published by Williams & Wilkins Co., Baltimore: 1942. Pp. 132; figures, 144. Price, \$7.50.

Gastro-intestinal Diseases. By various contributors to the Medical Clinics of North America. Published by Saunders. May, 1942. Vol. 26, No. 3. Pp. 350; illustrations, 21.

Memorable Days in Medicine. A Calendar of Biology and Medicine. By PAUL F. CLARK, and ALICE SCHIEDT CLARK, Department of Bacteriology of the University of Wisconsin Medical School. University of Wisconsin Press, Madison. Pp. 305, Frontispiece, 38 illustrations. First edition, 1942. Price, \$2.00.

Better than a day by day Medical History Calendar, this booklet presents for every day in the year one or more anniversaries of memorable events, with anything from a line to a page describing each event. It was published in briefer form in *Medical Life* in 1936-1937.

Doctor Bard of Hyde Park. By J. BRETT LANGSTAFF. E. P. Dutton & Co., New York: 1942. Pp. 365; illustrations, 12. Price, \$3.75.

Annual Review of Physiology. J. M. LUCK, Editor. Published by American Physiological Society, Inc. Pp. 709; figures, 2. First edition, 1942. Price, \$5.00.

Female Sex Hormone Therapy; The Follicular Hormone, Part I—(eighth edition), *Part II, the Corpus Luteum Hormone* (first edition). *Male Sex Hormone: Therapy: A clinical guide* (first edition). Set of 3 books issued by Shering Corp., Medical Research Division, Bloomfield, N. J.: 1941.

Medical Manual of Chemical Warfare. Reprinted by Permission of The Controller of His Britannic Majesty's Stationery Office. Revised edition: 1942. Chemical Publishing Co., Inc., Brooklyn, N. Y. Pp. 121; plates, 10. Price, \$2.50.

The Electrocardiogram and X-ray Configuration of the Heart. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P. Lea & Febiger, Philadelphia: Second edition, 1942. Pp. 404; figures, 108; illustrations, 163. Price, \$7.50.

Text-book of Pathology. By SIR ROBERT MUIR, M.A., M.D., Sc.D., LL.D., F.R.S. The Williams & Wilkins Co., Baltimore: Fifth edition, 1942. Pp. 991; figures, 599. Price, \$10.00.

Management of the Sick Infant and Child. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (England), L.R.C.P. (London), Dean Emeritus, University of California Medical School, and Professor of Medicine; Formerly Professor of Clinical Pediatrics, University of California Medical School; Formerly Visiting Pediatrician, San Francisco Children's Hospital; Formerly Member Health Advisory Board of the City and County of San Francisco; and WILLIAM E. CARTER, M.D., Director of University of California Hospital, Out-Patient Dept.; Formerly Chief of Children's Clinic, University of California Hospital; Formerly Attending Physician, Los Angeles County Hospital; Formerly Attending Physician, San Francisco Hospital, San Francisco. Published by C. V. Mosby Company. Sixth edition: 1942. Pp. 977; figures, 95.

Medical Application of the Short Wave Current. By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mt. Sinai Hospital, New York; Assistant Clinical Professor of Therapeutics, New York University of Medicine. Williams & Wilkins, Baltimore: 1942. Thoroughly revised, second edition. Pp. 344; illustrations, 87. Price, \$5.00.

Handbook of Hygiene. By JOSEPH W. BIGGER, M.D., Sc.D., F.R.C.P.I., M.R.C.P. (London), D.P.H., M.R.I.A., Professor of Bacteriology and Preventive Medicine, University of Dublin, Lieutenant-Colonel, Royal Army Medical Corps. Williams & Wilkins, Baltimore: Second edition, 1942. Pp. 414; figures, 13. Price, \$4.50.

Synopsis of Materia Medica, Toxicology and Pharmacology. By FORREST RAMON DAVISON, B.A., M.Sc., Ph.D., M.B., Medical Department, The Upjohn Company, Kalamazoo, Mich.; Formerly Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock: Second edition, 1942. Pp. 695; illustrations, 45 (4 color).

Textbook of Medical Treatment. Various authors. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), Professor of Therapeutics and Clinical Medicine, University of Edinburgh; Physician, Royal Infirmary, Edinburgh; and L. S. P. DAVIDSON, B.A. (Cambridge), M.D., F.R.C.P. (Edin.), F.R.C.P. (London), Professor of Medicine and Clinical Medicine, University of Edinburgh; Physician, Royal Infirmary, Edinburgh; Formerly Regius Professor of Medicine, University of Aberdeen; and J. W. McNEE, D.S.O., D.Sc., M.D. (Glasgow), R.F.C.P. (London) Physician, H. M. the King in Scotland; Regius Professor of Practice of Medicine, University of Glasgow; Physician, Western Infirmary, Glasgow; Consulting Physician, Univ. College Hospital, London. Foreword by the late PROFESSOR A. J. CLARK, B.A. (Cambridge), M.D., D.P.H., F.R.C.P. (London), F.R.S.; Formerly Professor of Materia Medica, University of Edinburgh. Williams & Wilkins, Baltimore: 1942. Second edition. Pp. 1179; several illustrations. Price, \$8.00.

Synopsis of Ano-rectal Diseases. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S., Ex-Vice-President, A. M. A.; Ex-Chairman, Section on Gastroenterology and Proctology, A. M. A.; Ex-President, American Proctologic Society; Chairman, American Board of Proctology, Inc.; Professor of Proctology, Wayne University; Fellow (Honorary) Royal Society of Medicine; Extra-Mural Lecturer on Proctology, Post-Graduate School, University of Michigan; Proctologist, Harper, Charles Godwin Jennings, and Woman's Hospitals; Consulting Proctologist, Detroit City Receiving Evangelical Deaconess, Wayne County Hospitals, Children's Hospital of Michigan, Detroit Tuberculosis Sanitarium, Detroit. C. V. Mosby Co., St. Louis: Second edition, 1942. Pp. 315; illustrations, 182; color plates, 12.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University, School of Medicine. Pp. 560; illustrations, 119. W. B. Saunders Co., Philadelphia and London: Third edition, revised, 1942. Price, \$5.00.

The book is practically the same as the second edition which appeared in 1938. The subject matter is treated superficially and from a practical standpoint. Recent developments in the field have not been incorporated in the book, so it would not be satisfactory as a textbook for medical students nor for practitioners who wish to bring their knowledge up to date.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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THE POSTERIOR PITUITARY GLAND.

THE activity and marked pharmacodynamic effects of extracts of the posterior pituitary were known long before the hormonal effects from many other glands were discovered. Yet, interestingly enough, only meager knowledge exists of the place of the posterior pituitary in physiology, while the place in physiology of many glands, the parathyroids and adrenals for example, is well established despite the fact that active extracts are of more recent origin and no more dramatic in their action. It was in 1895 that Oliver and Schafer⁵⁶ first demonstrated the vasopressor effects of pituitary gland extracts given intravenously, and in 1898 that Howell³⁸ showed that the effects rested in the fraction from the posterior lobe. In 1928, Kamm and his associates⁴¹ fractionated the extract of the posterior lobe and showed a dissociation between the pressor and oxytocic actions.

Anatomic Relationships. There is some confusion in the terminology applied to the posterior pituitary gland. To clarify these points a chart demonstrating the nomenclature, as suggested by Rioch and Wislocki and taken from the paper of Heinbecker and White,³⁴ is given below:

MAJOR DIVISIONS AND SUBDIVISIONS OF THE MAMMALIAN HYPOPHYSIS.

ADENOHYPHYSIS.

- | | | |
|-------------------|---|----------------------------------|
| Lobus Glandularis | { | 1. Pars distalis (anterior lobe) |
| | | 2. Pars tuberalis |
| | | 3. Pars intermedia |

NEUROHYPHYSIS.

- | | | | |
|---------------------------------|---|-------------------------|------------------|
| Lobus Nervosus
(Neural lobe) | . | 1. Infundibular process | } Posterior lobe |
|---------------------------------|---|-------------------------|------------------|

- | | | | | |
|--------------------------------|---|---|---|---|
| Infundibulum
(Neural stalk) | . | { | 1. Infundibular stem | } Neural stalk together with sheath of
lobus glandularis, designated as
hypophyseal stalk |
| | | | 2. Median eminence of
tuber cinereum | |

Histologically, the structures of the neurohypophysis consist of a group of cells, the pituicytes, which are closely related to neuroglia, and large masses of unmyelinated nerve fibers. A close relationship between the hypothalamus and the neurohypophysis seems evident.² Fibers originating in the supraoptic nucleus pass to the neurohypoph-

ysis, and Heinbecker and White,³⁴ in a careful study in dogs, concluded that the only nuclei unquestionably contributing fibers were the supra-optic and paraventricular. These relationships are most important in the consideration of diabetes insipidus to follow below, and further discussion concerning them will be found there.

Hormones. There has been much dispute concerning the origin of the hormones. For a long time reluctance to accept the neural elements as a source of glandular secretion upheld the intermediate lobe as the source. However, much evidence has accumulated to indicate that the neural elements, the pituicytes, are the source of the vasopressor, oxytocic and antidiuretic activities,^{7,25} whereas intermedin, the melanophore-dispersing hormone, comes from the intermediate or anterior lobe.

The chemical nature and actual number of the hormones are as obscure as their origin. The pressor, antidiuretic, oxytocic, and melanophore-dispersing principles are generally conceded to be separate entities. As just stated, the last named is thought to be from the median, or anterior, lobe, while the others are clearly posterior in origin. Likewise, from what has been said, it is clear that extracts have not been purified chemically. Best known of the highly purified fractions are the vasopressor and oxytocic principles separated by Kamm and his associates⁴¹ and by Stehle.⁶⁵ Electrophoretic studies^{14,39} indicate different rates of migration of pressor and oxytocic principles obtained from chemically untreated, mechanically expressed juice of fresh glands, and lend evidence to the idea that they are, in their natural state, separate chemical entities. Sedimentation by the ultracentrifuge⁶¹ indicates the large molecular size of these fractions, which exist either as a single large molecule or two separate large molecules, and also indicates a change in these structures by the technique of extraction, with the development of physiologically active split products.

The dramatic pharmacodynamic effects of the hormones of the posterior pituitary have led to widespread use of the extracts of the gland. In the United States Pharmacopœia XI, the preparation listed is *Solution of Posterior Pituitary*, or *Posterior Pituitary Extract (PPE)*. The action of this preparation is striking, especially on the renal, cardiovascular, and gastro-intestinal apparatus, as well as on metabolism, the lungs, the uterus, and on carbohydrate metabolism. It acts directly upon smooth muscle. Each one of these actions will be discussed below; and diabetes insipidus, because of its importance, will be considered as an entity following these discussions. The important clinical relationships are considered under each heading.

Renal Action. It has been suggested that the antidiuretic effects of PPE are generally associated with the pressor principle, and indeed the effect is shown clearly by pitressin. Some evidence points to the possibility that a separate principle, or at least one which may be dissociated from the pressor effect, may be responsible. Heller,^{35a} by use of thermal inactivation at various pH values, showed that vasopressor effects are lost at a more rapid rate than the antidiuretic effects. By making use of the difference in stability of the antidiuretic and vasopressor principles, he obtained preparations which contained only about 8 parts of pressor activity to 100 parts antidiuretic activity. These had the typical action of PPE on water diuresis and on the urinary chlorides of normal human subjects.

The renal effects of PPE are clear-cut. Ten units, 1 cc. of the so-called obstetrical preparation (1 unit equals the activity of 0.5 mg. of the standard powder), produces a marked reduction in urinary volume in normal individuals in the face of a high water intake.^{58,64} Similar effects occur in renal disease and diabetes insipidus, and the same inhibitory action is elicited in animals.^{52,63b} Present evidence points strongly to a primarily renal mechanism—increased reabsorption of water by the tubular mucosa, especially the proximal convoluted tubules and the thin portion of Henle's loop.^{10,26,63a} The other proposed theory is that of an extrarenal action on water exchange between blood and tissues. In some vertebrates, the bird for example, the quantity of glomerular filtrate is affected.

Increased reabsorption by the tubules has been related to the structure of the nephron in various vertebrates,¹⁰ and has been correlated with the development of the thin segment of the loop of Henle. Interesting in this light is the work of Heller.^{35c} He made a quantitative estimation of the antidiuretic activity of pituitary in a number of classes of vertebrates, mammals, birds, amphibians, teleost and elasmobranch fishes. Antidiuretic activity was present in the pituitary glands of all these groups, and in different species of the same class of vertebrates the glands were found to contain roughly the same amount of antidiuretic activity per 100 gm. of body weight. There was, however, a pronounced difference in the content in mammals and all other classes. Mammalian pituitary bodies contained at least 8 times as much antidiuretic principle per 100 gm. of body weight as the glands of non-mammalian species. A relationship was suggested between the phylogenetic development of Henle's loop and the amounts of antidiuretic hormone produced by the posterior pituitary, and a correlation of the development of an anatomic structure with that of a hormonal mechanism. Accompanying the reabsorption of water there is an increase in chloride output⁵⁷ attributed to a decreased tubular reabsorption of that ion.^{63a}

Certain conditions are known to influence the antidiuretic action. Boyd and Garand⁹ found that extremes of environmental temperature depress the water-retaining effects of PPE in rats. Water retention was more effective after prolonged dehydration and thirst. Administration of salt decreased, and even reversed, the water-retaining effect. Hickey, Hare and Hare³⁶ have shown that the state of body hydration influences the antidiuretic potency of the posterior lobe in rats. Dehydration diminishes the potency. They reviewed the literature on this subject.

The renal action of PPE is often described as the diuretic-antidiuretic action. There is much controversy concerning the diuretic action, and evidence points strongly to its being a secondary effect from pressor activity.^{35b} A diuretic hormone from the anterior lobe has been postulated, but Barnes, Regan and Bueno³ believe this effect results through thyroid stimulation, for it is inhibited by thyroidectomy in dogs.

Clinical uses of posterior pituitary extracts based on the antidiuretic effect have found an important place in the treatment of diabetes insipidus, and will be discussed under that subject. Recently attempts have been made^{57,58,64} to utilize the antidiuretic effect in concentrating the urine for a test of renal function. Results appear promising. Ten

units of PPE are given to an unprepared patient and 3 hourly collections of urine made. Normally, the specific gravity of one specimen reaches, or exceeds, 1.022. Pregnancy, marked oliguria, and hypersensitivity to PPE are contraindications. The test should be used with caution in patients with angina pectoris. (See Cardiovascular Effects.)

Cardiovascular Effects. These effects need little discussion from the clinical standpoint. Inspection of the patient following the injection of 10 units of PPE shows a distinct pallor, which can be interpreted only as the result of constriction of small vessels contributing to skin color. One would expect definite changes in the blood pressure, but such doses in man produce very little change.^{51, 54} In animals, the effects on blood pressure vary with many factors. In dogs, for example, marked rises occur, but the effects of coronary constriction may produce a decided drop. The studies of Grollman and Geiling⁵² indicate for a brief period a fall in pulse rate, O₂ consumption, and cardiac output, followed by a rise. These primary effects are interpreted as resulting from coronary artery constriction; the secondary effects from the accumulation of catabolites,⁴⁸ which brings about a condition of oxygen debt.

The importance of considering the results of coronary constriction must be kept in mind when PPE, or pitressin, is given to patients with arteriosclerotic heart disease. Where angina pectoris is the clinical manifestation of coronary arteriosclerosis, one would have the best clinical test of the importance of this effect and, indeed, if the drug is given to such patients, it should be administered with caution and with the antidote, epinephrine or ephedrine^{48, 49} at hand. PPE has been known to produce attacks of angina in patients with coronary arteriosclerosis. The Reviewer has administered 10 unit doses of PPE many times, without any harmful effects, to patients with coronary arteriosclerosis. Graybiel and Glendy²⁹ have found no significant cardiovascular symptoms in patients with arteriosclerotic heart disease with angina after slow intravenous infusion of a dilute solution of pitressin in doses adequate to produce pallor and uncomfortable abdominal cramps. Electrocardiographic changes resulting from administration of PPE have been described^{32, 48} and are thought to arise through stimulation of the cardio-inhibitory center, through vasoconstriction and inhibition of oxidative processes.

In spinal anesthesia¹³ posterior pituitary has been used with ephedrine to prevent a drop in blood pressure. Attempts to relate posterior pituitary activity to hypertensive states, including toxemias of pregnancy, are considered under Hyperfunction, below.

Effects on the Gastro-intestinal Tract. These effects depend largely upon the action on smooth muscle. In man there is an inhibition of gastric motility and a depression of gastric secretion following the administration of PPE. In diabetes insipidus,⁶ gastric symptoms are frequent. Changes in the gastric juice have been noted, including a higher degree of acidity, and a greater volume. Administration of PPE decreased these findings. In animals, gastric erosions and ulcers have been produced by the administration of pitressin, or PPE.^{5, 21} Local ischemia is the usual explanation.

Other evidence of a relationship between the posterior pituitary and gastric ulcer has been the finding of ulcer in association with pituitary

disease. The fact that PPE inhibits gastric secretion has led to its use in the treatment of peptic ulcer, while the association of gastric erosions with injections of extracts in animals has led, as stated above, to the idea of an etiologic factor for peptic ulcer in vasospasm, if not in the posterior pituitary. Interestingly enough, both of these concepts were discussed in succeeding issues of a recent journal.^{5,50}

Reports in the literature do not agree upon the effects of PPE on the intestine. Some of these differences are accounted for by variations in species, in technique, and in the part of the gastro-intestinal tract studied. In unanesthetized dogs, Larson⁴⁵ found that PPE, or pitocin, in intravenous doses of 10 milliumits per kilogram usually produced a decrease in tone and motility of the upper and lower portions of the large intestine; larger doses produced similar but more marked changes. Pitressin usually had no effect. Subcutaneously PPE and pitressin in larger doses usually caused an increase in movements in the upper portion of the large intestine with no significant effect on tone. In half the cases the lower portion was not affected. Pitocin subcutaneously in like dosage usually had either no effect or decreased the tone and motility of the large intestine.

In man, during operations on the abdomen,¹¹ marked spasm of the intestines with a concomitant peritoneal relaxation has been noted within 5 to 10 minutes after the intramuscular injection of pitressin. This effect is manifested in the usual patient by the act of defecation.

A number of uses have been found for PPE in the gastro-intestinal tract. These include the reduction of intestinal flatus in gall bladder visualization by Roentgen ray⁴³ and the control of postoperative distention.^{11,59}

Effects on Carbohydrate Metabolism. Hyperglycemic effects have been attributed to the oxytocic fraction,^{22,37} and it has long been known that PPE inhibits the hypoglycemia of insulin injections.^{22,31} Griffiths has studied this problem but finds no satisfactory answer. A direct relationship or antagonism is possible, or circulatory changes in the skin could decrease the absorption of insulin. Griffiths³¹ found that PPE inhibits hypoglycemia from subcutaneous insulin in rabbits, but in many animals the intravenous administration of insulin gave inconstant results. This suggests definitely the theory of decreased rate of absorption brought about by the vasoconstrictor effect of PPE.

Neufeld and Collip^{54a,b} brought forward evidence in rabbits and other animals to show the existence of a substance from the posterior lobe, not the pressor or oxytocic principle, which is antagonistic to the hyperglycemia caused by epinephrine.

Effects on Respiration. Laryngospasm, bronchoconstriction, and increased mucous secretion have occurred, especially in asthmatic individuals during anesthesia following pitressin.¹¹ Respiratory effects are described²⁵ as secondary to circulatory effects.

Effects on Blood. The pressor hormone causes hydremia or dilution of the blood,⁶⁹ with a fall in hematocrit, a decrease in specific gravity, and in total serum proteins.

Corey and Britton^{15b} have shown an antagonistic action of desoxycorticosterone and PPE on chloride and water balance. This report elaborates on former communications on the same problem from the same laboratory. In animals desoxycorticosterone was found to reduce

severely the output of urinary sodium, while PPE greatly increased its excretion. The authors feel that removal or deficiency of either cortico-adrenal or posterior pituitary tissues may produce disturbances in fluid and salt balance explicable on the basis of the remaining glands being unleashed or hyperactive. Both glands elaborate principles which specifically counteract or antagonize each other in their effects on fluid and electrolyte balance. For normal salt and water regulation in the body, a balanced relationship between the adrenal and pituitary mechanism seems essential.

Anemia is produced experimentally^{19,28} and is discussed further under Hyperfunction:

Effects on the Uterus. Geiling and Oldham,²⁵ in reviewing the evidence in the literature on the *in vitro* and *in vivo* experiments on the uterus, outline as follows the factors upon which the nature and degree of the reactions depend: (a) The species of animal; (b) the phase of the menstrual or estrous cycle; (c) whether the uterus is gravid or not gravid; and (d) the stage of pregnancy, whether early, late, in parturition, or in the puerperium. They point out that the reaction of the uterine muscle to pituitary preparations is markedly affected by the nature of the ovarian, placental, or anterior pituitary hormone whose influence is preponderant at the time of injection.

In human beings early in pregnancy, there is no reaction to pitocin, probably because of inhibition by the luteal secretion; there is a response to pitressin. Later in pregnancy, the reaction to pitocin returns. In parturition, the uterus is very reactive to pitocin and to PPE, a time when their use by obstetricians is widespread. In the puerperium again, there is little or no response to pitocin. This summary is taken from Geiling and Oldham.²⁵

Murphy, using the Lóránd tocograph, has studied variations in uterine response to PPE in certain stages of pregnancy. In one study^{52a} on 26 primagravidas, approximately 19 days before the onset of labor, PPE was given intramuscularly in small doses. Murphy correlated the responses with the duration of labor and found significantly shorter labors in those with a response. Under the conditions of his study he concluded that there existed a significant relationship between the character of the uterine contractile response to PPE, administered during late pregnancy, and the character of labor, as indicated by its length. In another report, the same author^{52b} studied 32 women with the same technique at regular intervals during pregnancy. In 2, a uterine response failed to develop at any time; in 29, a characteristic reaction occurred; and in 1, an unusual response was recorded. Typical responses included: 1, A series of clonic contractions at a rate of 20 per hour; 2, onset of contractions after the 25th week of gestation; 3, a wide variation in the time in pregnancy when contractions were first observed; 4, inconsistency with respect to appearance of contractions after they were first noted; 5, a shortening of the interval between treatment and onset of uterine response as pregnancy advanced; 6, a slowing of the contraction rate as pregnancy advanced; and 7, absence of unusual tension of the uterine wall before treatment. He concluded that patients vary widely in their response (uterine) to pituitrin during pregnancy; contraction patterns depend largely on the tension of the uterine wall.

The human non-pregnant uterus shows, surprisingly enough, a greater response to pitressin than to pitocin. Variations also occur in the different phases of the menstrual cycle. Interesting studies on the rabbit uterus⁸ show striking differences in sensitivity of different parts of the uterus to epinephrine and PPE. There is a relative insensitivity of the cervical end to PPE and sensitivity to epinephrine. The tissues in these studies were taken from uteri shortly before and shortly after parturition.

A preparation with such marked pharmacodynamic effects as PPE cannot escape widespread use. It has been used in all phases of pregnancy for over 30 years and hazardous results have been reported from the beginning.⁵³ In the first and second stages of labor, great danger to mother and child may develop with its use. Complications such as ruptured uterus, lacerated cervix, fetal death, and others have curbed its use in the induction of labor. After the second stage, it is widely used to shorten the placental stage and decrease bleeding, to hasten, if possible, involution and prevent infection, a point not entirely agreed upon,²⁵ and to prevent or control hemorrhage in therapeutic abortion. Conservatism requires that its use then be confined to hospital practice.

Hypersensitivity to PPE. Hypersensitivity to PPE has been reported on several occasions.⁴⁷ Symptoms include pallor, a drop in blood pressure, gasping respiration, urticaria and edema. The dramatic picture is relieved by epinephrine. So-called "pituirgin shock" is also infrequent, but not rare.¹ Adelman and Lennon noted 7 cases in 1 year. They frequently found pruritus, urticaria, and angioneurotic edema accompanying the shock.

Theories of the cause of pituirgin shock include histamine reactions, anaphylaxis, and cardiac effects. The preparations used by Adelman and Lennon are reported as histamine-free. A cardiovascular etiology is conceivable, for the effects of PPE on the coronary arteries could result in coronary constriction, myocardial anoxia, cardiac dilatation, and the picture of shock. However, the occurrence of urticaria and of positive skin tests for sensitivity to the preparation favors an allergic explanation. Skin reactions are apparently the result of some fraction other than the pressor or oxytocic principle.

Treatment of pituirgin shock includes intravenous fluids, oxygen, and epinephrine or ephedrine. The latter two drugs are effective in allergic states and, as stated before, in coronary constriction. They are contraindicated, however, in certain types of anesthesia, notably ether and cyclopropane,¹ when they should be omitted in treatment. Pituirgin shock has developed in patients under anesthesia, especially in the obstetrical use of PPE, as well as in its use in gynecologic surgery.

The physician administering PPE should be cognizant of these dangers and should be prepared for their treatment.

The Melanophore-dispersing Hormone. The dermal melanophore-dispersing hormone, so-called intermedin, is a product of the intermediate lobe. It causes pigment migration when injected into cold-blooded vertebrates. In mammals, which have no chromatophores, its importance is not established, but a metabolic rôle has been suggested. The origin and functions of this hormone are discussed by Kleinholz and Rahn.⁴⁴

Clinical Syndromes Related to Posterior Pituitary Dysfunction. Studies of the pharmacodynamic effects of PPE have not been accompanied by a clarification of the syndromes thought to be associated with posterior pituitary dysfunction. In most glands of internal secretion where functions have been ascertained, syndromes associated with hyper- and hypofunction are well known. This is not true with the posterior pituitary gland.

The Question of Hyperfunction. A large literature exists⁴⁶ on the possible relationship of pressor substances, particularly that concerned with the posterior pituitary, to eclampsia and other hypertensive states. No consistent findings have been reported. In the presence of eclampsia, or preëclampsia, doses of PPE already mentioned as not appreciably affecting the blood pressure produce sharp elevations in blood pressure,^{17,18} and diminish the urinary volume. The observation that preëclamptic women show such sensitivity while normal pregnant women do not has been the basis for a test to differentiate preëclamptic states. A positive test in the last trimester would lead to the assumption of the presence of preëclampsia. In 113 women, de Valera and Kellar¹⁷ did not think the results sufficiently consistent to justify the use of the reaction as a diagnostic test for preëclamptic toxemia. Although such reactions suggest the possibility¹⁸ that the posterior pituitary gland may, in some way, be associated with the disease, inconsistency in the reactions speaks against an important relationship. In other hypertensive states, similar associations have been postulated. Differentiation between pale and red hypertension on the basis of these reactions has been suggested, but this view does not represent the consensus.

Friedman and Prinzmetal,²³ using the denervated rabbit's ear sensitive to epinephrine in 1 to 100,000,000 dilutions and to pitressin in 1 to 150,000, found only 2 of 18 hypertensive patients with evidence of pressor activity in the blood exceeding that of those with normal blood pressure. Again results are conflicting and inconclusive. Certainly, posterior pituitary secretion may be important in such conditions when it reaches hyperactive structures, where deactivation does not occur, or where excessive amounts are put out, but proof for this point is not yet established.

Liu⁴⁶ points out that experimental hyperfunction produced by injection of hormones has been successful in a number of glands, such as the parathyroid and the islands of Langerhans. To be sure, this method has been used with the posterior pituitary. Injections in animals have produced the changes already mentioned (*r. supra*). To repeat, hypertensive pictures and gastro-intestinal changes develop. The latter findings include engorgement of the stomach with development of erosions. Some animals develop punched-out ulcers, at times even with perforation. Erosions of the stomach occur in many animals, and neutralization of the gastric acidity prior to the injection of the pituitary extract prevents the development of the lesions.¹⁹ It is the pressor principle that is gastrototoxic and the gastric effects apparently result from intense vasospasm with inhibition of blood flow.

Further remarks on gastric effects will be found under Diabetes Insipidus and under Effects on the Gastro-intestinal Tract.

Anemia of the macrocytic variety has been produced in rabbits by

large subcutaneous doses of PPE.^{19,28} It has been ascribed to increased blood destruction because of the accompanying reticulocytosis and increased bile elimination. Water retention has also been given as a cause,²⁸ but the problem is not settled.²⁰

PPE in large doses affects the kidneys, apparently through angiospasm of the renal arteries and arterioles.⁴⁶ Byrom¹² believes the changes in rats resemble those of eclamptic toxemia, with hypertension, delayed excretion of water, albuminuria, coma, catarrh and degeneration of the renal convoluted tubules. The parallel is interpreted as supporting the view that the lesions of eclampsia and preëclampsia are expressions of vascular spasm, but the hypothesis is rejected that such spasm is caused by simple oversecretion of vasopressin. Liu⁴⁶ points out the doubtful clinical significance of data such as the animal experimentation cited above. One would be on uncertain grounds in postulating that certain cases of peptic ulcer, macrocytic anemia, or renal disease result from hyperfunction of the posterior lobe. Dosage in the experimental animals has been tremendous. It is possible, as has often been stated, that the body may become more sensitive to posterior pituitary hormones and, in eclampsia for example, may react markedly to small amounts.

Jones⁴⁰ has described a syndrome which he considered was due to overactivity of the posterior pituitary. The patient showed hypertension, hyperchromic anemia, achlorhydria, and abnormal carbohydrate tolerance. An extract of the patient's urine disclosed a pressor principle,⁵⁵ an antidiuretic action on the rat, and presence of the melanophore-dispersing hormone. The effects of the extract were similar to those produced by the pressor principle of pituitary preparations. The pressor and antidiuretic substances in the urine very noticeably decreased with improvement of the patient.

The Question of Hypofunction—Diabetes Insipidus. Diabetes insipidus is generally considered as the outstanding expression of posterior lobe hypofunction. This condition is characterized by polyuria with a urine of low specific gravity and an increased thirst. A possible rôle of the anterior lobe in diabetes insipidus has been put forward, but all evidence points directly to the neurohypophysis.^{2,15a,25}

Dandy¹⁶ states that diabetes insipidus in man is caused by lesions in the environs of the hypothalamus and is pathognomonic of a lesion of some type in this general area, but that the present limits of the center are not established. Clinically, difficulties in establishing these limits lie in lack of localization of disease to areas sufficiently small; and, experimentally, difficulties also lie in localized damage, for surrounding structures may be injured. Dandy states as clinical facts that hypophyseal tumors confined to the sella turcica and not affecting the stalk or hypothalamus never induce diabetes insipidus, regardless of hypophyseal destruction, and operations on the human hypophysis for tumors are never followed by diabetes insipidus unless the stalk or base of the brain is traumatized. Still PPE usually controls the symptoms. Dandy quotes a case of Fletcher's²⁴ in which a small tumor at the base of the brain did not involve the hypophysis, and a case of his own in which section of the hypophyseal stalk without trauma to the base of the brain or hypophysis produced permanent polyuria and polydipsia.

In the rat²⁷ experimental diabetes insipidus results when fibers which innervate the parenchymatous cells of the neurohypophysis are destroyed, releasing the cells from nervous control. The cells atrophy, and when the number of inactive cells is large, compensatory hypertrophy appears. If enough secretion is produced, diabetes insipidus is only temporary. If not, persistent mild diabetes insipidus ensues. If the hypertrophied cells secrete to exhaustion, permanent diabetes insipidus appears.²⁷ In dogs,³⁴ diabetes insipidus results from complete interruption of the fibers to the neurohypophysis or from complete destruction of the neurohypophysis with only 3% to 10% of the pars distalis remaining. Maximum permanent diabetes insipidus may not result with failure to interrupt all fibers to the neurohypophysis or failure to remove it completely. These authors feel that confusion on this point results from failure to recognize that complete removal or denervation of the median eminence is a necessary condition for maximum permanent polyuria. They also present evidence that the cells of the supraoptic and paraventricular nuclei do not secrete pitressin, and that infection in the region of the hypothalamus can prevent the manifestations of diabetes insipidus, even in the absence of the entire neurohypophysis.

It is concluded that injury to the supraoptico-hypophyseal tract leads to atrophy of the neurohypophysis and that interruption of these nerve tracts produces degenerative changes in the pituicytes with the occurrence of symptoms of diabetes insipidus. Diabetes insipidus has been produced in many animals by interruption of the hypothalamico-hypophyseal tract in the posterior lobe, in the stalk, or at the supraoptic nucleus. Maximum and permanent diabetes insipidus follows removal or complete denervation of the entire neurohypophysis resulting in retrograde degeneration of the entire supraoptic nuclei and the rostral ventral portions of the paraventricular nuclei. Failure to interrupt fibers of even 15% of the cells innervating the neurohypophysis will prevent the development of permanent diabetes insipidus.

The necessity for participation of the anterior lobe in the development of diabetes insipidus is debated. In 9 dogs, Heinbecker and White³⁴ showed, by microscopically confirmed serial sections, that permanent diabetes insipidus followed complete destruction of the neurohypophysis with complete absence of the pars distalis. They feel that the view, based on clinical reports, that some tissue of the pars distalis is necessary for diabetes insipidus, is due to the fact that the median eminence probably remained. A phase, called normal interphase, exists in some experimental animals when fluid exchange approaches normal between the transient and permanent phases of polyuria. This was eliminated in animals when all pitressin-secreting tissue was removed. Heinbecker and White suggest that normal interphase results in injury to pitressin-forming tissue sufficient to prevent hormone secretion, leading to the development of transient polyuria. After the effects of trauma subside, secretion is resumed, to disappear again when degeneration of the pituicytes occurs. This sequence of events would divorce any explanation for normal interphase from the pars distalis.

Information such as the above indicates that, in the dog, the adenohypophysis is not necessary for the development and maintenance of a permanent diabetes insipidus. Keller⁴² also demonstrated in dogs that

a moderate diabetes insipidus can exist in the absence of the anterior lobe and indicated that the absence of diabetes insipidus following any hypophysectomy is evidence that functional antidiuretic secretory tissue remains intact. He suggests that the presence of a functioning anterior lobe may intensify the severity of the diabetes insipidus. Some of Heinbecker and White's data do not support this view. Baker and Craft² report a case with only about one-sixth of the anterior lobe remaining in the presence of severe and permanent diabetes insipidus. The anterior lobe deficiency was sufficient to give dwarfism.

In diabetes insipidus, polyuria and polydipsia are the characteristic symptoms. The question of which is primary, of whether increased urinary output follows thirst, or thirst water-loss through the kidneys, is important in understanding the mechanism of the disease. Richter⁶⁰ obtained evidence in rats to show that polyuria preceded the polydipsia and is the primary factor. The renal nerves play no part in the production of water diuresis in hypophysectomized dog.⁴

In transient diabetes insipidus, a substance has been found in patient's serum which inhibits the antidiuretic activity of PPE.⁶² This was not found in 2 patients with chronic diabetes insipidus. The urine of dehydrated normal dogs contains an antidiuretic substance; that of dehydrated dogs with diabetes insipidus, none.³³

From an investigation in patients with diabetes insipidus of the chloride and water intake and output with and without pitressin, White and Findley⁶⁸ concluded that there is no justification for division of cases into hyperchloremic-hypochloruric and hypochloremic-hyperchloremic types, or for the view that the condition is primarily a disturbance of the processes of exchange of water and salt between tissues and blood.

Nothing will be said here concerning standard forms of treatment with parenteral pitressin or PPE or the insufflation of powders into the nose. These forms of treatment are not always satisfactory because of side reactions, local irritation, gastric distress, and other symptoms. Therapy aiming at delayed absorption has been tried, as in the case of protamine insulin in diabetes mellitus or pellet therapy in Addison's disease. The object is delayed absorption with constant quantities which meets physiologic requirements.⁶⁷ Although inunctions have been tried, success has been outstanding with pitressin in oil subcutaneously.

Greene and January^{30a,b} implanted pellets of dried PPE in animals and patients. Inflammatory reactions limited their use. Pitressin tannate in peanut oil was then tried and was successful both in animals and patients. With 5 pressor units to the cubic centimeter, 1 cc. doses ameliorated symptoms for 30 to 82 hours. There were no unpleasant or deleterious general or local reactions. The effect on the manifestations of the disease was equal to that of other preparations of PPE and without disagreeable side effects. Stephens⁶⁶ found that 0.1 % zinc acetate prolonged and intensified the effect of aqueous solutions of pitressin, but that pitressin in oil gave a more marked prolongation and intensification of the effect.

Thorn and Stein⁶⁷ also tried pitressin tannate in oil. They found in 3 patients that a dose of more than 0.25 to 0.30 cc. daily should not be continued unless the clinical condition of the patient is being followed

closely. Larger doses may be given safely when treatment is administered only once in 48 hours. Control of polydipsia and polyuria was most satisfactory with treatment once daily. Pitressin tannate settles out of oily solution so that the preparation must be shaken vigorously when used. Failures in treatment have occurred without this precaution. Complications in Thorn and Stein's hands were water intoxication with excessive dosage and increase in the amount and duration of the menses in 2 patients.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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REVIEW OF SHOCK THERAPIES FOR THE MENTALLY ILL.

SINCE the introduction of insulin, metrazol, and electric shock in the treatment of the mentally ill, a tremendous amount of work has been done with these procedures. This work has not been confined merely to the treatment and results of the methods from a psychiatric viewpoint, but has produced far-reaching investigations by workers in allied fields of medicine. For instance, the physiologist has become interested in the mechanism which produces the coma; the biochemist is interested in studying the various chemical changes which take place during therapy; the neuropathologist is concerned with the pathologic changes that occur during and after the therapy; the internist is concerned with the problem of "punishment" that the body is forced to absorb during the actual treatment; the psychologist is absorbed in following the psychologic changes which take place under the influence of the treatment; the orthopedist desires to know the type of fractures occurring during insulin, electrical and metrazol therapy; the neurologist studies the influence of these therapies upon the organic nervous system; and the psychiatrist attempts to explain the manner in which the psychosis is altered.

The interest in this subject is testified to by the large bibliography which has been developed within the past 6 years. Jessner and Ryan^{30a} report 353 individual articles in their recent book, *Shock Treatment in Psychiatry*. The yearbook *Neurology, Psychiatry, and Endocrinology* has abstracted 68 articles since the treatment began in 1936.

Even though the original enthusiasm associated with the use of shock therapies has not been sustained, there is ample evidence that these treatments will continue to exert a certain amount of influence upon therapeutic procedures in the psychotic groups until newer methods of greater efficacy are introduced. One cannot say that the therapy offered the schizophrenic prior to the use of shock therapy was impotent; however, whatever therapy was used it was certainly less dramatic

in its immediate results. Psychotherapy, at best, is a slow and tedious procedure, and in some institutions utterly lacking. The introduction of a tangible, easily administered therapy was grasped by many. Such procedures have been adopted in private clinics, psychopathic and state hospitals. Not all the work by these various groups has been reported, but a considerable amount of this work has been published.

We⁵⁵ have recently analyzed 239 articles published in 39 English language medical journals during the past 6 years. We found that shock therapy may be roughly classified as follows (figures in parenthesis indicate the number of publications dealing with the topic listed):

1. General discussions on the use and results of insulin, metrazol, and electric shock (92).
2. Technique of administration and general management (22).
3. Complications (24).
4. Electrocardiographic and electroencephalographic findings (7).
5. The *modus operandi* (13).
6. Psychologic factors (12).
7. Follow-up studies and prognostic factors (6).
8. Physiologic, pharmacologic, pathologic, or biochemical aspects (34).
9. Neurologic effects (7).
10. Miscellaneous factors (20).

For our present discussion we have attempted to review the literature available to us on all these topics except items 8, 9 and 10.

General Discussion on the Use and Results of Insulin, Metrazol and Electric Shock. We⁵⁵ found that about one-fifth of the papers⁵² are concerned with the results of therapy, and of this number about 30 express a favorable opinion regarding the efficacy of the treatment. The others end on a vague note of optimism and suggest continued experimentation in this field. In only 1 paper³⁷ did the author feel that insulin treatment had not been proven. On the contrary, he raised considerable doubt as to its value.

Reports upon the results of therapy vary widely. In the first place the number of cases reported varies from 1 to 1039 per paper. Of the 50 papers, 33 report results on less than 100 cases, and are markedly optimistic on the basis of a small series. Recovery rates are reported from 92.3% to 7%, with an average of 52%. It is probably unsound to compare too closely the recovery rates on any two sets of studies from different hospitals since the criteria and definitions of "recovery" are individual with each hospital. In this connection we agree with Low³⁸ who states that recovery rates are reliable only when studied in relation to the adjustment of the patient after discharge.

In general most workers reporting seem to agree that the following factors are necessary for the most satisfactory results from shock therapy: 1, An illness of acute onset and short duration, preferably under 6 months, not longer than 1 year. 2, The presence of affective factors in the psychosis. 3, An adequate prepsychotic personality. 4, The presence of exogenous, as opposed to endogenous, precipitating factors. 5, An attempted heterosexual adjustment. 6, The absence of hallucinations and dereistic thinking.

The literature dealing with the general discussion of these therapies is interesting in that the authors attempt to confirm or disprove the

efficacy of these therapies. On the whole there is a fairly optimistic tone sounded in favor of these treatments. As Nation⁴³ reports, "... in this modern day every patient is expected to receive some form of therapy where possible, rather than depend on spontaneous remission." Sakel unwittingly spanned a gulf which some have felt existed between psychiatry and the rest of medicine by the introduction of insulin therapy. In this connection Sakel⁵⁶ states, "... it has become apparent that in the solution of these problems (of insulin therapy) psychiatry will be brought to medicine and medicine will come to psychiatry."

The belief that insulin is of benefit in the treatment of the schizophrenic is expressed by Easton¹³ who states, "It appears to me that in insulin we have a drug by means of which we can alter the clinical picture in schizophrenia. Whether the treatment ever becomes established time alone will tell. I do not believe the drug is specific in its action, but it seems to affect the patient in such a way as to make him more accessible and hence responsive to other recognized forms of treatment, such as occupational and psychotherapy. The latter are very necessary adjuncts to the treatment. The personality of the physician and nurse will both be reflected in the results obtained. I am firmly convinced that one can do more for schizophrenics with insulin than is possible without it."

Young⁶⁶ expresses his opinion after using insulin and metrazol for 3 years by saying, "It must be said that this brief and superficial accounting of experiences with the newer pharmacologic methods of treatment in the schizophrenic and depressive psychoses shows them to be a valuable adjunct and an advance in therapy. . . . In the schizophrenic groups insulin or metrazol, or a combination of the two, are effective therapeutic agents, but it should be emphasized that the patient must be treated early. . . . Metrazol has been particularly effective in the treatment of the depressive reactions. . . . Finally, no matter how striking the results of any special method, treatment must continue along broad lines which focus the interest of the physician upon the patient and his adjustment to life situations, past, present, and future."

Early in 1936, Wortis reported upon the use of insulin therapy, and concluded with the remark, "The insulin treatment of schizophrenia promises to be either an unusual medical fiasco or a most remarkable discovery." Some 15 months following this statement Wortis^{65a} felt the latter prediction was more likely to be true.

The general "feeling" that insulin is of value has been expressed by Strecker⁶¹ in his statement, "While keeping in mind that after a certain duration of illness good results are obtained in a minority of cases, the results obtained in the first year of illness, at any rate, and probably also in the second, indicate that there is some real value in insulin treatment. It is only natural that those who have seen many new treatments come and go should wish to reserve their judgment, but I believe that most of those who have used or witnessed this therapy themselves cannot help feeling that it does constitute a decided advance in the treatment of schizophrenia."

Ross⁵² summarizes the results of both insulin and metrazol therapy as follows: "Beneficial results from treatment of all cases of dementia praecox of no matter what duration with insulin are much greater than

the results of the untreated group. The results of treatment with insulin are much better than the results obtained from cardiazol alone. Combination of cardiazol with insulin apparently assists the action of the insulin in selected cases. Treatment with camphor is not recommended by those who have used it in New York State Hospitals. The results obtained in cases where the duration is over 2 years not only justified the expense and time, but show it would be an error to neglect such cases. The recovery and improvement rates are progressively less according to the duration of the illness. The dangers of insulin therapy in the hands of experienced and trained physicians are almost negligible. An active educational campaign should be carried on, so that an early diagnosis of dementia præcox can be made and treatment instituted at the earliest possible date."

Bond, Hughes and Flaherty⁹ concur in these favorable impressions, but they sense the necessity of follow-up, and something of the difference of opinion that arises in establishing the diagnosis of schizophrenia. They report, "In every hospital using insulin-shock, the patients treated should be followed for 5 years. Another group of patients, or other groups, as near alike as possible should be followed for the same time as controls. It seems certain that relapses after favorable responses will follow in all groups. In the valuable paper just published by Malamud and Render it is stated that a study of the course and prognosis in schizophrenia should include the criteria used by the author in diagnosis. We take a little exception to this statement because it might give encouragement to more varying personal standards for schizophrenia. After all, it is safer for the psychiatrist to use the criteria put down in the official *Statistical Manual*, and to work toward a definition which all can use. Insulin-shock therapy is not a complete answer. But the transformation of the patient's condition is so immediate and favorable in a majority of cases that it will have place in, or provide suggestions for, a further therapy, and this without regard to whether good results last for an afternoon or indefinitely. It is only fair to remember that Sakel spoke of insulin-shock as the artillery in a general combined attack on the disease process. Insulin in convulsive doses alters the metabolic processes of nerve."

The reports thus far cited have dealt with the physicians' ideas about the therapy. It is interesting to learn what the patient has to say about the treatment. Starks⁶⁰ has reported that patients "... receiving insulin have little if any objection to the treatment and have no memory of a fear reaction. All but a small percentage of patients receiving metrazol find the treatments unpleasant and object to them in varying degrees. Of the metrazol-treated patients, one-fourth admitted fear of death in connection with the injections. All but 6 of the 47 patients receiving metrazol recognized that they were being treated for their sickness. These 6 interpreted the treatment as punishments. In many of those experiencing a fear of death and in all who regarded the treatments as punishments, it was possible to correlate these reactions with previously existing morbid trends. Both drugs, whether used solely or successively, give rise to a feeling of increased physical vitality, reduce emotional tensions, promote lucidity and a realistic outlook on life, and assist in reintegrating intrapsychic and

ERRATA

Page 141—Heading *should read*:

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.

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DIRECTOR, COLORADO PSYCHOPATHIC HOSPITAL, DENVER, COLO.

AND

GEORGE S. JOHNSON, M.D.

PROFESSOR OF PSYCHIATRY, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

Page 142, 37th line—*reads*:

from 92.3% to 7% with an average of 52%.

Should read:

from 7% to 92.3%, etc.

Page 147, 38th line—*reads*:

extensive treatment with thiamin bichloride, etc.

Should read:

extensive treatment with thiamin chloride, etc.

Page 147, 42nd line—*reads*:

administration of protamine, etc.

Should read:

administration of potassium, etc.

Page 148, 17th line—*reads*:

collapse, and changes in the control nervous system, etc.

Should read:

collapse and changes in the central nervous system, etc.

Page 148, 21st line—*reads*:

The death rate from shock therapies shows a low incidence of 23 per 10,000 patients, etc.

Should read:

The death rate from shock therapies shows a low incidence of 73 per 10,000 patients, etc.

Page 148, 11th line from bottom:

Reference No. 42 should be No. 44.

Page 149, 30th line—*reads*:

tion; auricular extrasystoles, shifting forewaters, etc.

Should read:

tion, auricular extrasystoles, shifting pacemaker, etc.

Page 152—References:

Reference 11 *reads*: Cleckley, Bowles and Metter; *should read*: Cleckley, Bowles and Mettler.

Reference 24 *reads*: Hemwich; *should read*: Himwich.

Page 153—Reference:

Reference 47 *should read*: Piotrowski, Z.: (a) Psychsom. Med., 1, 508, 1939;
(b) Psychiat. Quart., 15, 807, 1941, etc.

psychomotor processes. Both drugs pave the way for more effective psychotherapy."

Young and Young⁶⁷ see a certain danger in allowing our interest to become too diffuse in the search for some answer to the schizophrenic problem when they say the "... use of these methods carries the danger of arousing special interests along associated biochemical, physiologic, and neuro-anatomic lines. While such studies are necessary and informative, one should attempt to understand the changes of functioning of a part in terms of the integrative relationship of all the parts. There is also the danger of disregarding former disciplines and replacing them with a set of facts based on new methods of treatment. We feel that, no matter how striking the results of any special method, treatment of psychiatric disorders must continue along broad lines which focus the interest of the physician on the patient as a psychobiologic unit with complex sets of integration, functioning in a variety of life situations, past, present, and future."

Technique of Administration and General Management. The technique and general management of the shock therapies have varied a great deal since the original description outlined by Sakel and Meduna. The majority of authors outline their general procedures and stress any variation from the original methodology and phenomenology of these therapies. Variations on an original method seems to be one of the ways in which we try to progress in medicine, and a number of papers testify to this fact.

In the field of insulin therapy the following variations have been observed: 1, Protamine zinc insulin has been used by many workers who are in agreement with the conclusions drawn by Reese and Vander Veer,⁵⁰ "Protamine zinc insulin is not suited to hypoglycemic shock therapy for schizophrenia because (a) the effects of equal doses are not always the same; (b) the dose must be constantly varied, since no uniform shock dose can be established; (c) closer laboratory coöperation, with frequent determinations of the blood sugar, is required with this compound than with regular insulin; (d) the danger of after-shock is greater; and (e) epileptiform shocks are somewhat more frequent. Shock therapy with protamine zinc insulin differs from that with regular insulin, since (a) with large doses the fasting (morning) sugar level declines steadily, and (b) it is almost impossible to produce comatose wet shock."

2. The usual intramuscular route has been replaced by the intravenous route in some clinics with the following results: Jones³¹ reports that coma is produced more quickly; however, same amount of insulin is required by the intravenous as by the intramuscular route.

Sherman, Mergener and Low⁵⁷ compared the effects of coma doses of insulin administered intravenously and subcutaneously to psychotic patients and found the following: "In a group of 13 schizophrenic patients the blood sugar fell more promptly in response to coma doses of amorphous insulin given intravenously than to those given subcutaneously. The fall in blood sugar in response to coma doses of insulin given intravenously occurs at about the same rate as in response to small doses, *e. g.*, 10 units. In the latter case the blood sugar returns to normal values rapidly, whereas in the former it stays low for a prolonged time, so that coma ensues. The only practical advantage of

the intravenous administration of insulin is the shortening of the pre-coma period. There was no appreciable difference in the coma doses required between the two methods of administration. There was no significant difference in the complications resulting from the two methods of injection. Spontaneous emergence from coma produced by intravenous insulin is rare."

Polatin, Spotnitz and Wiesel^{48a} set out to produce insulin coma as quickly as possible and with a minimum of coma. They chose the intravenous route of administration and found that 48% of patients treated 2 weeks or longer showed improvement. They felt this route of administration had numerous advantages over the usual hypoglycemic shock technique. The shock period was shortened; patients recovered spontaneously from the shock to drink the dextrose solution; none of the patients had convulsions or received any detectable injury; the total amount of insulin per patient was less than that required subcutaneously to produce coma; a minimum of nursing supervision was necessary.

Polatin, Spotnitz and Wiesel^{48b} extended the uses of intravenous insulin to ambulatory patients with mental disease. In a group of 18 patients they found that mild hypoglycemic shocks were of considerable value. They reported that in "81% of the patients so treated there was definite improvement. The beneficial effects are slowly cumulative. It was also observed that in some cases of dementia præcox this therapy is necessary over an indefinite period of time in order to maintain such patients on some level of social adjustment. This form of therapy warrants further investigation as to its effects upon the disorders of the central nervous system."

3. An interesting use of insulin has been the administration of subshock doses to schizophrenic patients. Bennett and Miller⁵ found that subshock doses of insulin were of value in controlling most of the problems of management of uncoöperative patients, and corrected difficult feeding problems. They did not consider this therapy curative, although in their series many favorable remissions did occur. In addition to the papers already mentioned, other papers have dealt with interesting phases of insulin technique. For instance, McGregor and Sandison⁴⁹ report the use of potatoes used in connection with sugar in the interruption of the coma. They, too, report the intravenous route of administration with an average saving of 46.6% of insulin.

Hunt and Feldman²⁸ have pointed out that more rapid absorption appears to take place if the sugar solution is well-diluted and warmed before tubing the patient to terminate the insulin shock.

4. The most interesting variation in the administration of both metrazol and electric shock has been the introduction of curare by Bennett.^{3a,b,4} The introduction of this drug made it possible to continue the use of metrazol and electric shock without the danger of inducing the fractures so prone to occur in these treatments. Bennett has also used scopolamine in the convulsive therapies and reports: "Intocostrin (standardized curare) is a valuable adjunct to convulsive therapy in that it removes the danger of fractures, particularly the vertebral type, sprains, backaches, and other unpleasant complications which have occurred in this type of treatment. It makes it possible to apply the therapy to mental cases who would be deprived of it because of some skeletal defect. Scopolamine is effective in reducing appre-

hension and post-convulsive restlessness in patients receiving convulsive therapy, particularly in those who have had no previous fear reactions. The combined effect of scopolamine and curare has been found almost completely to eliminate post-convulsive excitement."

Complications. The complications of the shock therapies have presented many problems, some of which have been solved, and others which have not been adequately explained. Probably the most serious complication of these therapies has been the injury to the skeletal system. Polatin, Friedman, Harris and Horwitz^{49a} reported that of 173 patients treated with hypoglycemic shock therapy, 62 (36%) manifested epileptoid convulsions. Of these patients who were available for roentgenographic examination, 34 (20.5%) revealed compression fractures of the vertebræ. The same authors reported^{49b} an incidence of 43.1% compression fractures in 51 cases treated with metrazol therapy. Along with the compression fractures of the vertebral bodies, fractures and dislocations of other bones have occurred. Femur, humerus and scapula have been fractured, while jaws and shoulders have been dislocated. The technique of administration has been altered in an effort to lessen the incidence of fractures. Curare has been very effective in preventing fractures; however, in our own clinic compression fractures of the vertebræ have occurred in 2 cases prepared for electric shock therapy by curare.

In addition to the use of curare as a means of protecting the skeletal system, other devices such as braces, casts, or specially designed beds to insure adequate hyperextension have been introduced.

The prolonged hypoglycemia, seen in most clinics treating patients with insulin shock, is probably the second most frequent complication. Some workers have suggested that protracted shocks should be induced for therapeutic reasons; however, Kant³² cautions against such a procedure since he feels that in protracted shock there lies a danger of permanent organic brain damage. Lester³⁵ studied a series of cases suffering from a prolonged insulin coma and reported a mortality rate of 16%. He urged the avoidance of such a complication, and concluded that such a complication was not followed by improvement. Although a few dramatic improvements have occurred, prolonged coma should not be induced. Cleckley and Templeton¹² have witnessed prolonged non-hypoglycemic coma in 6 cases which failed to respond to extensive treatment with thiamin bichloride, nicotinic acid and riboflavin. Two of the cases came to autopsy; however, no adequate cause was found for the failure to awaken. Since prolonged coma is an unpredictable and dangerous complication, they advise the routine administration of protamine to all patients who develop this complication. Likewise they suggest riboflavin, nicotinic acid and thiamin chloride be used prophylactically in all cases undergoing treatment. The clinical signs seen in cases of prolonged coma have been explained by Binzley and Anderson⁶ on a basis of actual cellular pathology. They consider the process to be an encephalopathy caused by interference with normal oxidation processes. Frostig¹⁹ feels that the protracted shock occurs only in cases where the medullary phase was allowed to develop and persist for some time. In explaining this phenomenon, Frostig first places emphasis on the disturbed function of the medullary

nuclei, and second he feels that the continued carbohydrate deprivation of the control cells is a factor.

Epileptiform seizures frequently occur as a complication in the course of insulin shock therapy. Goldman²¹ analyzed 3119 periods of hypoglycemic shock and found that the convulsion in hypoglycemia is a characteristic of individuals and not the method. Individual susceptibility varies greatly. Therapeutic benefits from this type of convulsion are questionable; however, cases have been seen to improve following a convulsion during hypoglycemia coma. Finiels¹⁶ reports such a series of cases in which convulsions occurred either spontaneously or were induced by metrazol. He felt that the occurrence of convulsions during the actual coma enhanced the value of the therapy. This is not the general consensus at the present time. Laryngeal spasm,²⁰ subarachnoid hemorrhage,¹⁷ cerebral insult,³⁴ status epilepticus²⁰ and anaphylactic response²⁵ have been mentioned as further isolated complications of insulin therapy. Likewise, pulmonary edema, cardiac collapse, and changes in the control nervous system have been stressed by O'Neil⁴⁵ who observes that considering the amount of insulin administered, and the repetition of the treatment, it is remarkable that complications have not been more frequent.

The death rate from shock therapies shows a low incidence of 23 per 10,000 patients treated with insulin, and 23 per 10,000 patients treated with metrazol as cited by Kinsey.³³

Considerable experimental animal work has been performed in an effort to ascertain the effect of the shock therapies on the central nervous system. Arieti¹ reported on 5 monkeys after metrazol-induced convulsions that the changes were not always proportional to the number of convulsions. Pathologic changes when found consisted of small groups of cells which presented acute degenerative changes, or, in some cases, the severe type of degeneration described by Nissl. In 2 cases anemia of the external cortical layers, anemic and hyperemic foci in the inner areas and generalized breaking up of the network of capillary blood columns were observed. These changes were considered functional and not responsible for the cellular lesions.

Cleckley, Bowles and Mettler¹¹ observed more striking changes in animals treated with metrazol. The lesions noted consistently appeared to be secondary to vascular constriction or vascular changes. No direct relationship existed between the degree of neuropathologic change and the total amount of metrazol; however, the degree and extensiveness of the lesions corresponded in general to the number and severity of the seizures.

Neuburger, Whitehead, Rutledge and Ebaugh⁴² induced electrical convulsions in 12 mongrel dogs. The findings were less severe than the changes found following metrazol injections. In the latter, the most important lesion is in the cerebral cortex. More or less complete necrosis of the nervous parenchyma was observed in small circumscribed areas.

Not all the deaths resulting from these therapies have been studied histologically, but sufficient numbers have been studied to give a glimpse of what happens to the brain. Weil and Liebert⁶⁴ studied 6 patients treated with metrazol injections and found the outstanding histopathologic features to be marked hypertrophy and hyperplasia of

astrocytes and, to a lesser degree, of the microglia. Involvement of the ganglion cells was less pronounced, although in 1 case of involutional melancholia there was generalized severe degeneration of the neuron with neuronophagia. These changes show a striking similarity to the changes found in experimental animals.

Jansen and Waaler²⁹ reported pathologic changes in 6 schizophrenics and 1 depressive who had been treated with insulin. In 3 of the cases the cause of death was considered cerebral in nature. In 1 of these cases the brain changes consisted of ischemic alterations in the cortex, diffuse proliferation of glia and slight vascular changes. In the other 2 cases, the changes included more extensive ischemic necrosis of the cortex in the frontal and temporal lobes, partly with hemorrhagic infarction. In the other 4 cases, there were only isolated subarachnoid perivascular effusions of blood and hyperemia.

Ebaugh, Barnacle and Neubuerger¹⁴ report 2 deaths resulting from electric shock. In the first case, a man 59 years old suffering from a depression, the cause of death was due to coronary occlusion and myocardial infarction. In the second case, a man 52 years old, and suffering from a manic reaction, the general autopsy findings were negative. It was assumed the total outcome was due to postconvulsive respiratory arrest. Both cases showed rather widespread, but not serious, histologic changes in the brain.

Electrocardiographic and Electroencephalographic Findings. Closely allied to the complications frequently observed in shock therapies are the changes seen in the electrocardiogram and the electroencephalogram. Bellett, Freed and Dyer² took tracings on 40 patients during 58 shock treatments, and noted changes in two-thirds of the cases. These changes consisted of depression of the ST segment, diminution of the height of the T wave, prolongation of the QT interval, auricular fibrillation, auricular extrasystoles, shifting forewaters, sinus arrhythmia and sino-auricular heart block.

Messinger⁴¹ reports that the most frequent electrocardiographic abnormalities in hypoglycemia are seen to be flattening and inversion of T waves and sinus arrhythmias. Other changes which have been noted are pathologic "q" waves, changes in R and S voltage, slight widening of the QRS complexes, appearance of "V" waves, appearance of auricular and ventricular extrasystoles. Goodrich and Smith²² believe that the most frequent electrocardiographic change associated with prolonged insulin hypoglycemia is a lengthening of electrical systole. They further state that important electrocardiographic changes do not occur during severe hypoglycemic coma, nor does repeated hypoglycemia produce any persisting changes in the electrocardiogram. Sonenthal and Low⁵³ are in agreement with these statements and go further in stating that electrocardiographic records following investigations of metrazol and insulin treated patients reveal no evidence of myocardial damage months after termination. Electrocardiographic studies were made on 50 schizophrenic patients treated with metrazol by Levine, Piltz and Reznikoff.³⁶ One hundred electrocardiograms were taken, 50 before and 50 after treatment. In only 2 patients were the changes considered significant and in each case they were believed to be transient.

Measurement of brain potential during insulin hypoglycemia has

been reported by Hoagland, Rubin and Cameron.²⁶ In a series of 35 tracings taken on 6 patients during insulin shock they report a progressive decline in alpha-wave-frequency of some 40%, which parallels with a time lag of some minutes the declining blood sugar curves. Sugar injected during coma restores the frequency along a smooth curve. The alpha-frequencies are believed to be directly proportional to the rate of carbohydrate metabolism of the cortical cells producing the rhythm. It is interesting that the same authors,²⁷ reporting later on the "Delta Index," stated that in the schizophrenic patients treated with hypoglycemic shock they have found no special brain curves qualitatively different from those found in normal persons.

Modus Operandi. Perhaps the most fascinating question raised by the shock therapies is the manner in which improvement occurs or the *modus operandi* of the shock therapies. No one has hit upon an explanation which has met with the approval of the majority, but certain theories have appeared and reappeared which warrant our attention.

The fundamental physiologic mechanisms involved in shock treatment are unknown, but the diminution or suspension of brain metabolism during treatment seems significant.^{65b} Freudenberg¹⁸ states that, "Although the metabolic findings in schizophrenia are not absolutely specific, the following hypotheses concerning its basis and the mechanism of cure can be regarded as established. In schizophrenia there is probably a primary disturbance in cerebral respiration, perhaps due to some lack of oxygenating substances. This disturbance leads to a collection of toxic products, probably originating from the protein metabolism. Insulin therapy induces the oxybiotic processes necessary for detoxication and also an irritation of the cell membranes, which results in an increased exchange between the cells and their surroundings. Similar but more sudden changes take place in cardiazol therapy."

On the basis of observations of clinical symptoms, cerebral oxygen utilization, blood sugar level and electrical activity of the brain, Himwich, Frostig, Fazekas and Hadidian²⁴ were able to conclude that as a result of the hypoglycemia caused by the administration of insulin, the metabolism of the brain is diminished.

Spiegel and Spiegel-Adolf⁵⁹ attempt to explain the convulsions in metrazol and insulin therapy due to an increase in the permeability of the cellular surface films. This increase facilitates the exchange of ions between the cytoplasm and its environment and the removal of products of its metabolism.

Many are not satisfied with even this partial explanation on a physiologic or organic basis, and they therefore propose a theory on a psychologic basis. Improvement is considered due to the patient's experience of the treatment as a threat to his existence, or as punishment, or as death and rebirth.

Jessner and Ryan^{30b} feel that hypoglycemia changes the organism in such a way that the patient becomes able to turn his affection and his interest to persons and objects of the outside world and so to give up his narcissistic isolation. Whether this altered attitude is merely temporary or becomes permanent depends greatly upon his capacity to endure reality, with its alluring and threatening qualities.

The status of our understanding of the *modus operandi* is best summarized by Müller's⁴² statement, "Neither the endocrine phase of the

treatment nor brain pathology, nor the question of convulsions, nor the soothing, quieting effect, nor failing consciousness, nor the potent psychic shock . . . is alone sufficient to solve our problem."

Psychologic Factors. Various psychologic tests^{7,46,63} have been used to determine the changes which take place during treatment, and on the whole these tests tend to indicate what benefits may be expected of the treatment. The Goodenough test¹⁵ has shown that some patients have been harmed by the therapy instead of helped.

The Rorschach test has been used to show improvement following therapy,^{23,47a} to predict the outcome of therapy, and as a prognostic guide.^{47b,c} Piotrowski^{47d} claims that if only those patients who show that color has meaning for them were treated, the percentage of improvements would be increased.

Follow-up Studies and Prognostic Factors. Coupled with the Rorschach test, good clinical practice and observation are of great value in predicting the outcome of the schizophrenics treated with insulin. According to Cheney and Clow¹⁰ the dementia præcox patient who has the best outlook for recovery or improvement following insulin therapy is a male under the age of 30 who has had a comparatively adequate prepsychotic personality, whose psychosis had an abrupt onset with a definite external precipitating cause. He will have been sick less than a year before the institution of treatment; he will have shown an excited catatonic state without evidence of what we have called deterioration, which is defined as consistent lack of attention to personal habits, bizarre behavior, disconnected thinking, and apathy. Conversely, the patient not likely to benefit by hypoglycemic treatment will be a female over 30 who, with an inadequate personality, insidiously and without definite external precipitating cause, has developed over a period of more than a year before treatment a mixed form of dementia præcox with evidence of deterioration as defined above. Of great significance is Cheney's remark that patients who will benefit by insulin treatment will have the same characteristics as those benefited formerly with other forms of treatment. This supports our conviction that insulin does not have a specific curative effect, but that it may bring about changes that accelerate or facilitate improvement in those who have the constitutional capacity for such improvement or recovery.

Wall⁶² found in a study of 37 schizophrenics that those cases which showed typical schizophrenia, presence of considerable emotional reaction, a history of some attempt at sexual adaptation, and manifestation of sexual interest in the psychotic state would be benefited by insulin shock treatment; whereas those patients who reacted poorly to the treatment showed the following factors: "Very frequently came from a poorly integrated family with little solidarity among its members. In many instances as children they were considered in some respect different from the other siblings. They adapted to school in a somewhat worse than average fashion and showed a lack of ambition. They showed very little sexual interest prior to the psychosis and there were no overt sexual manifestations other than autoeroticism during the psychosis. Almost all of the patients who exhibited autistic behavior (mannerisms, grimacing, posturing, etc.) failed to respond. They showed a picture of typical schizophrenia without extraneous admixtures."

Rymer and Ebaugh⁵⁵ noted that follow-up reports on the shock therapies are relatively scarce, and the majority of these are reported for only short periods, although many workers warn against interpreting results based on too brief study. Malzberg,³⁹ in a series of 1039 schizophrenics in the New York State Hospital set-up, found that the number of patients who had been reported as "recovered" at the termination of their insulin therapy remained constant at the end of the first year, but that the percentage "improved" dropped from 65.4% to 49% during this period. However, this represented a significant improvement over patients with schizophrenia who did not receive insulin shock therapy. In a later article, he and his coworkers, Ross, Rossman, Clive and Schworer,⁵³ report that records and results are so poorly standardized that little can be concluded as to the real efficiency of insulin therapy, and they urge the establishment of "uniform criteria for the interpretation of the results of treatment."

Ruslander⁵⁴ in a series of 55 cases treated with insulin found that 44% of the cases were sufficiently well to be discharged at the expiration of 1 year's parole. He noted a lack of improvement in patients ill longer than 18 months. Robinson⁵¹ reports 90% "excellent results" in 13 patients 18 months after treatment. Bond⁸ followed a group of 125 patients for 2 years and found that while one-half of all patients treated showed improvement at the termination of treatment, one-half of these had relapsed by the end of the second year. Somewhat better results were obtained in cases with an acute onset: two-thirds of these showed improvement, although one-half had relapsed at the end of the second year. Rymer and Ebaugh⁵⁵ in reporting the follow-up of 400 cases treated with shock therapies draw no conclusions as to the superiority of this type of treatment over that of careful non-shock therapy, but believe that the work is still experimental and requires intensive study on comparable groups over long periods.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MAY 19, 1942

Acetate and Intestinal Motility. J. F. McCLENDON, JOHN SCOTT, W. C. FOSTER and MORTON J. OPPENHEIMER (Laboratories of Physiology, Hahnemann Medical College and Temple University School of Medicine). The senior author¹ suggested that the laxative action of "roughage" is due to carbohydrate fermentation (acetate). In testing this hypothesis we found that we could increase the weight of the feces of a rat 10% by feeding acetate but 1000% by feeding agar or

¹ McCleendon: *J. Biol. Chem.*, 87 (Proc. XXIV, vii), 1930.

alginic acid (although these are to a large extent broken down by fermentation in the gut and the bulk of the feces cannot be ascribed to unaltered "roughage"). The difference is probably due to the fact that acetate fed as such is totally absorbed in the proximal part of the intestine whereas the acetate arising from fermentation of "roughage" is continually produced through the whole length of the intestine. Balloons were introduced at various levels into gut of trained or anesthetized dogs or rabbits and acetate introduced in the region of the balloon or elsewhere. The frequency of contractions remained constant but they varied in amplitude. The pH of the acetate did not seem to make a difference. The moderate pressure in the balloon was itself a stimulus to increased amplitude and was kept as constant as possible during an experiment. When the acetate reached the region of the balloon a greater effect on amplitude was obtained than when the balloon was in a Thiry-Vella fistula to which the acetate had no access. Even when the balloon pressure was minute or negative (Biebl exteriorized gut) the acetate increased the amplitude. Sixty cc. of N sodium acetate given by stomach tube to a fasted dog caused it to defecate in 25 minutes and 100 cc. caused another to vomit in 12 minutes.

Studies in Serum Protein Fractionation by Salt Precipitation in Infants and Children. MILTON RAPOPORT, MITCHELL I. RUBIN, and DORCAS CHAFFEE (The Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania School of Medicine). Plasma proteins of healthy and diseased infants and children were determined, using both the Howe technique and the phosphate precipitant of Butler and Montgomery. Fibrin was also determined.

Blood fibrin in healthy children was constant at all age levels studied, having the same value in premature infants as in older children. Total protein increased progressively with age, as did albumin and globulin. The albumin value attained the adult level in early infancy (2 months), but the globulin values were still significantly low at 11 months of age. There was a constant reduction of a globulin fraction precipitating between 1.2 and 1.6 molar concentration of the phosphate precipitant, through the entire period of infancy.

In *glomerulonephritis*, blood fibrin is elevated at all stages of the disease. In chronic *glomerulonephritis* there is reduction of the globulin and albumin, and also of a globulin fraction precipitating between 1.2 and 1.6 molar concentration of phosphate precipitant; this same fraction is increased in acute *glomerulonephritis*, returning to normal with complete recovery from the disease.

In the *nephrotic syndrome*, plasma fibrin is increased and serum albumin markedly reduced. Even though globulin was normal by the Howe technique, a reduction in the globulin fraction precipitating between 1.2 and 1.6 molar phosphate precipitant was found.

Reproduction and Lactation of Mice on Highly Purified Diets. CLAIRE FOSTER, JAMES H. JONES, FRIEDA DORFMAN and RUTH S. KOBLER (Departments of Pediatrics and Physiological Chemistry.

University of Pennsylvania School of Medicine). Mice have been raised to the fourth generations of offspring on a basal diet composed of purified fibrin 25 %, salt mixture 4 %, regenerated cellulose 4 %, and glucose 67 % with the following supplements added to 100 gm. of the basal diet in the amounts indicated: Linoleic acid 2 ml., alpha-tocopherol 6 mg., crystalline vitamin A 100 γ , naphthoquinone 5 γ , calciferol 2.5 γ , thiamine hydrochloride 1 mg., riboflavin 1 mg., pyridoxine hydrochloride 1 mg., calcium pantothenate 6 mg., nicotinic acid 6 mg., inositol 6 mg., para-aminobenzoic acid 15 mg., and choline chloride 60 mg. Fertility as determined by litters born per females mated and by size of litters was about equal to that of animals on a good stock diet but growth and survival to weaning were definitely below normal. The subnormal growth became more noticeable as the number of generations increased until in the F_3 generation the young were so small at the weaning age of 21 days that many of them removed from their mothers at that time died. Two females of the F_3 generation were mated and gave birth to 15 young of which only 2 survived to weaning. In all 73 females were mated and 63 litters were born totalling 447 young. Of these, 272 (61 %) were weaned. This compares with the weaning of about 85 % on our regular stock diet. Whether the ultimate failure depends upon an insufficient amount or an imbalance of the presently recognized factors or the absence of an unknown factor remains to be determined.

The Relation Between Oxygen Consumption and Cardiac Output in the Presence and in the Absence of Cardiac Disease. ISAAC STARR and LEON JONAS (Hartzell Department of Research Therapeutics and William Pepper Medical Laboratory, University of Pennsylvania). The change in the amount of the circulation for a given change in O_2 consumption has long been of interest.

Assembling the experiments of numerous investigators in which O_2 consumption was increased by exercise, Boothby and Rynearson drew a straight line through the data. This line was not a calculated regression; it indicated that when the O_2 consumption doubled the circulation increased by about 60 %.

This relation has also been investigated in hyperthyroidism. For a doubled oxygen consumption Liljestrand and Stenstrom found the circulation to increase about 120 %; Fullerton and Harrop about 138 %; and Boothby and Rynearson about 72 % on the average. Combining the data of the last two papers the line drawn by Boothby indicates approximately a 1 to 1 relationship between increases in circulations and O_2 consumption.

All these data may be criticized, for as the value for the O_2 consumption was a factor in the authors' estimate of the circulation in the cardiac output methods employed, so O_2 consumption and circulation (as calculated) were not independent variables and the relation between them was forced.

We have data in 32 cases of thyroid disease without cardiac complications in which the estimations of O_2 consumption and cardiac output were completely independent. The calculated regression of these data

passes almost exactly through the origin and its slope is close to unity. The correlation coefficient is 0.84, any value over 0.28 being significant.

We also have similar data for 28 cases of advanced heart disease. This regression passes below the origin and its slope is close to 0.5. The correlation coefficient is 0.69, any value over 0.32 being significant.

We conclude that, if the heart is normal, changes of metabolic rate in thyroid disease are accompanied by similar percentage changes in the circulation, a conclusion not far from the average result of our predecessors. In heart disease changes of metabolic rate are accompanied by changes in the circulation about one-half as great.

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RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (sic) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal of the American Medical Association* with its large circulation, will also emphasize the point.

We would like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, i.e., that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” give the more exact meaning.

THE EDITOR.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

AUGUST, 1942

ORIGINAL ARTICLES.

RHEUMATIC HEART DISEASE COMPLICATING PREGNANCY.

A STUDY OF 61 FATALITIES.

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IN Philadelphia during the decade 1931 to 1940 there has been no significant decrease in the maternal death rate due to rheumatic heart disease. The rate has remained between 2 and 3 per 10,000 live births for the greater part of the 10-year period. This record offers a striking contrast to the reduction in the total maternal death rate during the same 10 years. The latter rate has shown a steady decline from 7.9 deaths per 1000 live births in 1931 to 3.1 in 1940.

We have been interested, therefore, in determining whether the incidence of maternal deaths due to rheumatic heart disease has been reduced to a minimum, and, if not, whether means might be found for preventing fatalities resulting from this disease.

Method. Through the courtesy of the Maternal Welfare Committee of the local County Medical Society, the abstracted case records of all maternal deaths occurring in Philadelphia during the decade 1931 to 1940 were examined. The records of patients having heart disease or suspected of having it were segregated. After further reference to the hospitals' or physicians' records of this group, a selected list of cases was obtained which met certain requirements. First, the presence of rheumatic heart disease had been established by adequate clinical or postmortem evidence; and second, death had resulted primarily from the heart disease or from an

obstetrical procedure employed because of it. The study was limited to the rheumatic form of the disease because this is the principal form of heart disease encountered in women of childbearing age; it is responsible for the great majority of maternal deaths due to heart disease.

In the decade under consideration, there were 307,015 live births and 1789 maternal deaths in Philadelphia. Of these there were 61 cases which met the above requirements and are the basis for this analysis.

Preventability of Deaths. Of the 61 deaths in this series, 20 were regarded as preventable by the Maternal Welfare Committee.* In addition, a number of cases which were judged as non-preventable did not receive ideal care as outlined by such authorities as Stander and Kuder¹⁰ and Hamilton,^{4b} and from this point of view, may also have been preventable. Therefore, it is evident that the maternal death rate in Philadelphia due to rheumatic heart disease can be further reduced.

What then can be done to reduce this rate? Our study attempts to show the manner in which the deaths occurred and, in addition, certain of the important factors contributing to the fatalities. By so doing, it is our purpose to reëmphasize some of the special problems which must be successfully combated in the treatment of pregnant cardiac patients in order to lower the death rate among this group.

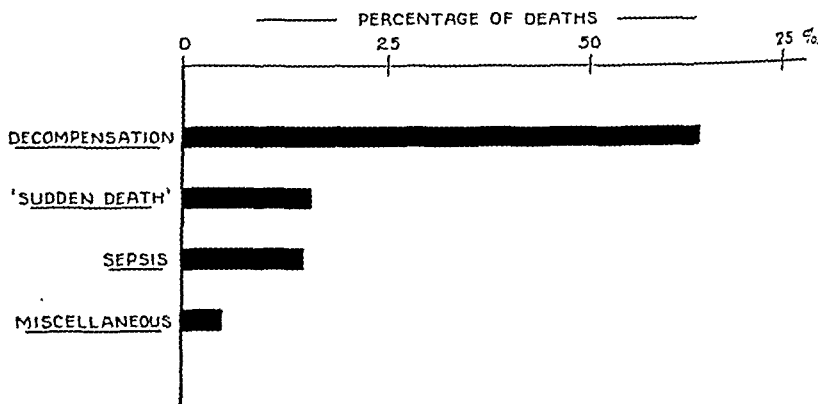


FIG. 1.—Distribution of maternal death according to the type of death.

Manner of Death (Fig. 1). Cardiac decompensation, including pulmonary edema, accounted for 39 (64%) fatalities. Sudden exitus, as from embolism, accounted for 10 (16%) deaths; this group probably also included several instances of acute congestive failure. Puerperal sepsis with terminal cardiac failure was responsible for 9 (15%) deaths. Of the remaining 3 (5%) fatalities, 1 was due to

* Since 1931, each maternal death which has occurred in Philadelphia has been analyzed and discussed by this committee. Decisions are thereby reached as to the preventability of the death and the factors responsible for it.

subacute bacterial endocarditis, 1 to acute antepartal endocarditis and 1 to an uncertain cause.

Relationship of Death to Pregnancy and Delivery (Figs. 2 and 3). Fifty-two (85%) of the patients died after the 28th week of gestation and 41 (67%) after the 35th week. Although it is apparent that death was generally delayed until the late stages of gestation,

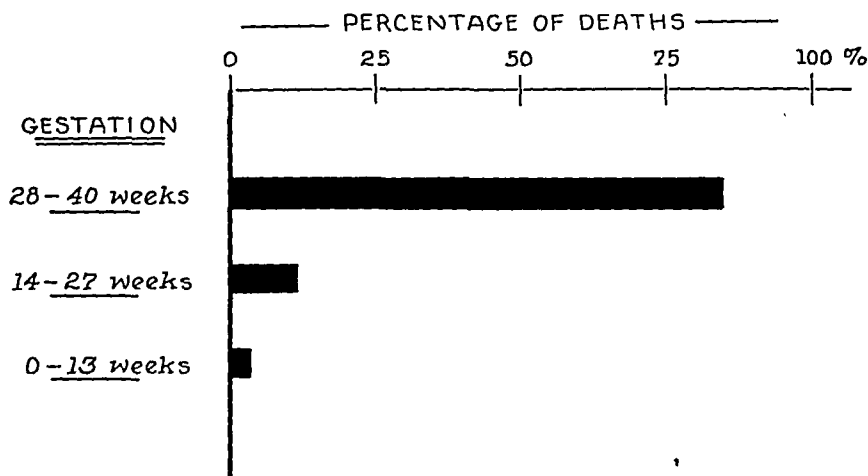


FIG. 2.—Distribution of death with respect to the duration of gestation.

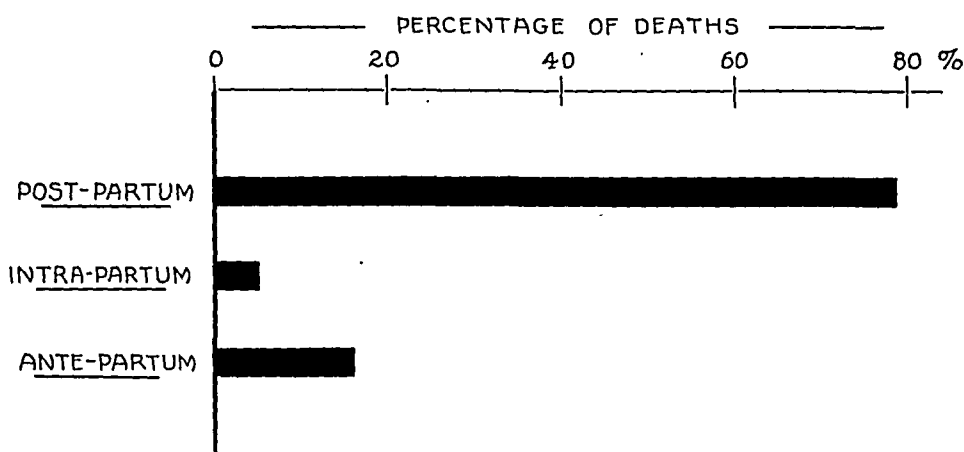


FIG. 3.—Percentages of deaths in pregnancy, labor and puerperium.

it did not usually take place while the patients were gravid. Forty-eight (79%) of the fatalities followed delivery. Furthermore, 23 of these fatalities occurred in the first 24 hours postpartum. Therefore in our series, the first postpartal day is the most critical period of the childbearing act for these women. In contrast to this, the period of labor was relatively benign, since only 3 (5%) of the fatalities occurred at this time. That normal labor, at least in the first stage, does not critically increase the work of the heart, was further suggested by the fact that we found little evidence of increasing cardiac distress during labor. We have emphasized only the first

stage of labor, since the second stage was in most instances extremely short, either because of the normal course of labor or due to prompt operative termination of it.

Relationship of Death to the Cardiac Status. Since the majority of the fatalities in this series occurred following delivery, it seemed advisable to consider them in relation to the condition of the patients immediately before delivery. In most instances, insufficient information was available on the patients' records to enable us to grade their cardiac status according to the classification proposed by the American Heart Association. We have, therefore, classified them into three groups, graded as follows: Grade I includes patients who had maintained cardiac compensation throughout pregnancy; Grade II, those who showed symptoms or signs of congestive heart failure at some time during pregnancy, but who had regained a state of compensation before delivery; and Grade III, those who were suffering from frank congestive failure at the time of the termination of their pregnancy.

The distribution of 44 postpartal fatalities according to our classification is shown in Figure 4. Only 10 (23%) were Grade I

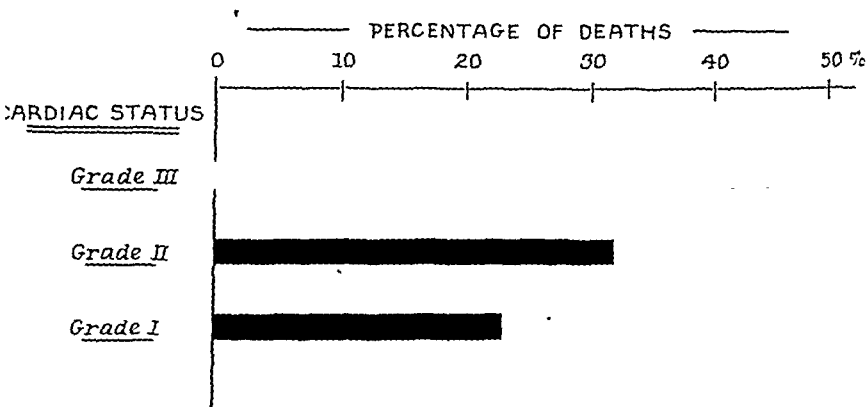


FIG. 4.—Distribution of postpartal deaths according to the cardiac status prior to delivery.

cardiacs, while 14 (32%) were Grade II, and 20 (45%) were Grade III. Moreover, approximately three-fourths of the fatalities in the last group (Grade III) occurred in the first 24 hours postpartum, and were the result of cardiac decompensation. In contrast to this, only one-fifth of the cases in Grades I and II died immediately postpartum. The majority of deaths in these latter two groups were due to delayed congestive failure, to some unavoidable cardiac accident, or to sepsis.

Method of Delivery. Of the 48 patients dying postpartum, 25 were delivered *per vaginam* and 23 by Cesarean section. The majority of Grade III cardiacs were delivered by section while the greater number of Grades I and II fatalities were delivered vaginally. The distribution of the cases according to the manner in which death

occurred and according to the time relationships of death to pregnancy and delivery was, with one exception, similar for the two groups: there was only 1 death from sepsis following vaginal delivery in contrast to 6 following Cesarean section.

Comment. Since, during the decade under consideration, only 61 cases were found which fulfilled the criteria as outlined for this study, it is evident that heart disease, even in a city where rheumatic heart disease is endemic, is not a frequent cause of maternal mortality. It is equally clear, however, that every gravid woman with organic heart disease represents a potential fatality from her cardiac lesion and therefore requires special care and consideration during her pregnancy.

The results of this study confirm, in general, the findings of previous investigators. The fatalities were principally due to congestive heart failure following delivery at or near term. If there is to be a significant decrease in the maternal death rate among cardiac patients who are permitted to attempt childbearing, it must come through a prevention of congestive failure.

The prevention of congestive heart failure prior to delivery is largely a problem in prenatal care. It means bringing each patient to delivery in the best possible cardiac status. The prevention of congestive failure and death after delivery is directly related to this status at the time of delivery. This is illustrated by our data, wherein it has been shown that almost 50% of the postpartal fatalities occurred among women who were decompensated at the onset of labor or at the time when termination of the pregnancy was undertaken.

Most of the fatalities occurred after the 35th week of gestation. This is probably not to be explained by the stress of advancing pregnancy, *per se*, since Cohen and Thomson¹ have shown that the cardiac burden imposed by pregnancy decreases after this time. Moreover, from this study the burden of labor or the strain of operation did not seem to be critical. Even among those patients bordering on congestive failure prior to labor or operation, death or signs of increased cardiac distress seldom appeared during the actual labor or delivery. Confirmatory evidence for this observation has been furnished by Hamilton and Thomson,⁵ Irving,⁷ and Gorenberg and McGleary,³ all of whom have noted that congestive failure rarely occurs during labor, and implied that labor usually does not critically increase the work of the heart. On the other hand, Stander⁹ and Jensen⁸ believe that "labor carries a real danger of congestive failure to the cardiac patient." This moot question deserves further study.

Our data suggest that emptying the uterus is the primary factor precipitating death. This concept is supported by the following: First, the largest percentage of deaths from congestive failure in any 24-hour period occurred in the first 24 hours following delivery, a period during which usually no other primary factor excepting the

physiologic readjustment of the circulation has had time to exert its effect. This relationship held true irrespective of the type of delivery or the cardiac status at the time of delivery. Second, the histories of some of these patients stated that there was a definite, and at times dramatic, increase in cardiac distress occurring promptly following delivery.

A number of hypotheses have been proposed to explain the mechanism of this phenomenon. We favor the concept that the emptying, and subsequent contraction of the uterus, forces blood from the large uterine vessels and sinuses into the general circulation. This autotransfusion seemingly cannot be properly distributed by a damaged heart and congestive failure may result. Nearly 30 years ago Hirst⁶ wrote, "The most dangerous period (in the pregnancy of the patient with valvular heart disease). . . is just after expulsion of the child, when the circulation is much disordered and an extra quantity of blood is thrown back upon the heart." We are aware of no investigations wherein this clinical observation has been tested. On the basis of this hypothesis, Hirst recommended venesection—a procedure which appears to be entirely reasonable. Hamilton and Thomson⁵ have tried the effect of applying tight abdominal binders immediately after delivery. The rationale for this was to improve venous circulation by augmenting the respiratory excursions of the chest walls and the diaphragms. Since we have not had personal experience with either of these procedures; we are content to present them without recommendation, *pro* or *con*.

From a study of fatalities alone, such as ours, we can make no definite statement concerning the relative merits of delivery *per vaginam* or by Cesarean section. It is evident that the typical cardiac death may follow Cesarean section as well as vaginal delivery. The incidence of fatal sepsis following Cesarean section, however, is much higher than that following vaginal delivery. Hamilton,^{4a} Danforth,² and more recently Gorenberg and McGleary³ have emphasized the dangers of sepsis and other complications following delivery of the cardiac patient by section. In view of these facts, and since the cardiac burden imposed by labor did not appear to be critical, it would seem that vaginal delivery is the method of choice for the majority of cardiac patients uncomplicated obstetrically.

It is likely that the mortality rate due to rheumatic heart disease complicating pregnancy can be lowered. From this study certain recommendations seem justified: It is necessary to bring the patients to delivery in the best possible condition. This can be done by early recognition of the heart disease; strict supervision of the patient's activities by both an obstetrician and cardiologist; and the prompt recognition and treatment of congestive heart failure. Immediate therapy of intercurrent infection, and hospitalization prior to expected delivery are useful measures. Partial digitalization prior to delivery is probably a wise precaution. It seems advisable,

furthermore, to defer delivery, if possible, while the patient is decompensated, and in general to deliver her by the vaginal route. Postpartum, signs of decompensation must be anticipated, and treatment promptly instituted if they appear. Since intravenous fluids may precipitate congestive failure, they should be avoided, particularly within the first 24 hours postpartum.

Summary. 1. Sixty-one maternal deaths due to rheumatic heart disease in Philadelphia during the past decade have been studied in reference to their preventability, manner of death and certain factors influencing the deaths.

2. Analysis of the manner in which death occurred among the cases studied indicated that the fatalities due to this disease resulted principally from congestive heart failure following delivery at, or near term.

3. Of the factors influencing death, the most important one amenable to control was the cardiac status of the patient at the time of delivery. Since this is almost solely dependent upon prenatal care, a significant decrease in the number of maternal deaths due to rheumatic heart disease can only be attained through an improvement in this care.

Acknowledgment is made of the valuable assistance rendered by Dr. Mary M. Livezey in reviewing hospital records for us.

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THE RECOGNITION OF VIRUS TYPE PNEUMONIA.

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THIS report consists of a survey of 52 cases which have been diagnosed by clinical means as "virus type pneumonia." The condition is a distinct disease entity and it is becoming evident that a

concept of the main features of this type of pneumonia is a valuable asset in the diagnosis and treatment of pulmonary disease.

In general hospital experience various types of pneumonias are encountered—pneumococcus, tuberculous, hemolytic streptococcus, staphylococcus, Friedländer's bacillus and *B. tularensis* and so on. Another interesting and rather common form of pneumonia has been previously described and designated by many different anatomic terms. Our experience with the clinical recognition of virus type pneumonia dates back to 1938 following the report by Reimann¹⁴ of a respiratory disease characterized in some instances by pneumonia and by recovery of a pneumonotropic virus.

This variety of pneumonia, and its differing aspects from other more well known and readily classified pneumonias, has attracted considerable attention. Endemics of this respiratory disease have been reported since 1935, when Bowen² recorded his observations on 89 cases of pneumonitis occurring among the troops stationed in Hawaii. The disease was mild and characterized by leukopenia, cough, spotty shadows in Roentgen Ray, few physical signs other than râles and without identifying organisms in the sputum. The author represented the occurrence of pneumonitis to be a complication of influenza. Another report of a similar nature was published by Allen¹ from Fort Sam Houston. It is interesting to note that by purely inductive reasoning Dr. Allen postulated the etiologic agent to be a virus. Accounts of outbreaks at Oregon State College¹¹ and Cornell University¹⁷ have been published and call attention to the ease of transmission of the disease.

Reimann,¹⁴ previous to these latter reports, described a similar disease of considerably more severity than that elsewhere reported. Eight cases of tracheobronchopneumonia, consisting of patients who became very ill with dyspnea, cyanosis, rather prolonged fever and marked sweating, were described. Reimann also pointed out that in some cases the clinical course was biphasic, so that it might in this respect resemble psittacosis. The character of the disease suggested to him that the etiologic agent was a virus. In a later report Reimann and Havens¹⁵ discussed 407 cases of acute respiratory disease of which 25 presented pneumonia and were more severely ill than those with tracheobronchitis. Interesting descriptions of the clinical aspects of this disease were published in 1940 by Kneeland and Smetana⁷ in New York City, where 52 cases with 1 death were observed, and also by Longcope⁹ who encountered 32 cases with 2 deaths during an outbreak at Baltimore.

The chief obstacle facing investigation of the etiology of this disease has been in the finding of laboratory animals which regularly exhibited pneumonia after intranasal inoculation with throat washings. In 2 of Reimann's first group of cases Stokes, Kenney and Shaw¹⁵ obtained results in experimental production and serial passage of pneumonia in ferrets. Later, Reimann reported indiffer-

ent results using a similar technique in 11 of the cases from the 1939 epidemic. Weir and Horsfall²¹ repeated inoculation experiments, using ferrets as well as a great many other animals without success in demonstrating pathogenicity until they used the mongoose. This animal was shown to be very susceptible to the virus and convincing serial passage was reported. Eaton, Beck and Pearson³ obtained different animal inoculation results but again showed a virus from cases of atypical pneumonia. Not only do these three separate investigations indicate a virus agent for this type of pneumonia but they also reported dissimilarity to other standard virus strains. Filter-passing differences and varying animal pathogenicity may possibly suggest the existence of more than one strain of a pneumotrophic virus capable of producing a distinct clinical type of pneumonia in humans.

The confusion in the literature of this type of atypical pneumonia is no wise lessened by the numerous anatomically descriptive names: "Acute Diffuse Bronchiolitis,"¹⁰ "Acute Interstitial Pneumonitis,"¹⁷ "Acute Pneumonitis,"¹² "Atypical Pneumonia,"^{3,12} "Bronchopneumonia,"^{6,8,9,11} "Disseminated Focal Pneumonia,"¹⁶ "Influenzal Pneumonitis,"² "Benign Bronchopulmonary Inflammation,"¹³ and others.

The protean character of the disease as to the type of cellular reaction within the respiratory system is suggested by the variety of descriptive names mentioned. While awaiting additional proof of the etiology of the disease, the name applied is less important than its clinical recognition as a disease entity. The varieties of pulmonary involvement do not permit an anatomic designation, whereas many features consistently present justify the designation virus type pneumonia.

This report is not a review of old hospital records to include cases of atypical pneumonitis with the intent of re-analysis. Only such cases are included as have come under our observation since 1938, within a period following Reimann's first report. The disease is becoming more common and is frequently being encountered. In this 34-month period at the Henry Ford Hospital in respect to in-patients, this condition was seen almost one-fifth as often as pneumococcus pneumonia. In the last 6 months, from April to October, the proportion of virus type pneumonia to pneumococcus pneumonia has been approximately as 6 to 7.

Seventy-nine cases have been recognized as definitely belonging to this group. Our experience is described in reference to only 52 consecutive cases where the period of observation and the absence of history of preëxistent respiratory disease renders the facts more suitable of analysis.

For convenience, the cases may be divided into three groups: 25 were mildly ill, 17 moderately ill, and 10 severely ill. Chart 1 summarizes certain features of one of the first cases recognized as suffering from this disease. Although the patient was critically ill,

leukocytosis was not present during the first week, and bradycardia was persistent. Repeated sputum examinations revealed no pneumococcus on direct typing and only commensal organisms were noted on sputum culture.

In previous reports the mild character of the disease was frequently stressed. Of the 52 patients here reported there were 10 who became seriously ill, 4 of whom showed an illness of critical proportions.

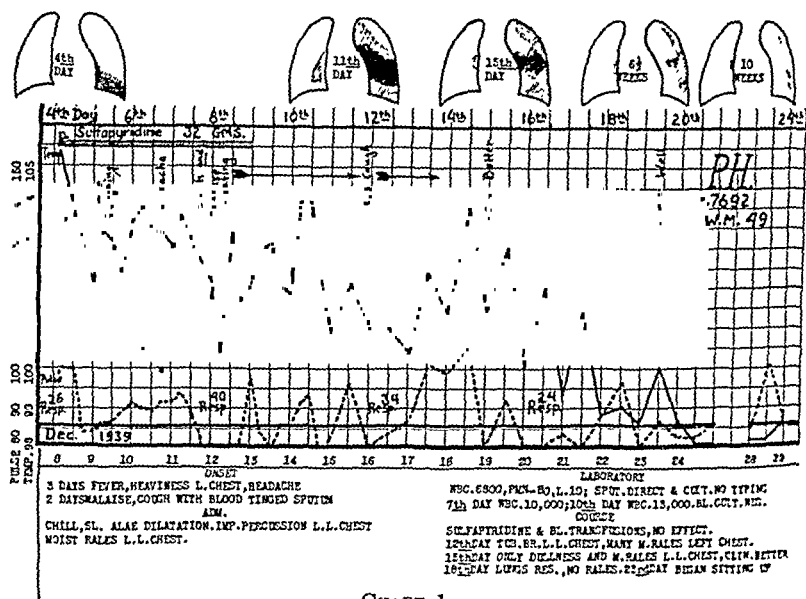


CHART 1.

The disease was, generally speaking, noted in young adults previously in good health. The average age of the group was 27.7, the oldest patient being 52 and the youngest 9; 50% occurred in the decade from 21 to 30.

The onset was generally insidious and was marked by the development of a cough which eventually became productive and was associated with some discomfort in the chest. Chilliness occurred in those more severely ill, but frank chills were encountered in only a few instances. Headache, while not always present at the onset, often became an important feature and assumed distressing proportions after the second or third day of the disease. Malaise and anorexia were present in a minor degree, but either or both were marked in about one-third of the patients. Two individuals in whom joint pains were salient complaints were initially suspected of having rheumatic fever.

Mucopurulent sputum, either white or yellowish, was most frequently mentioned; pink sputum containing small streaks of blood or even large amounts of red blood was also noticed. Only 3 patients

described rusty sputum. In almost one-fourth of the cases no sputum was present in significant amounts.

By the time the patients appeared at the hospital, usually on the fourth or fifth day, a variable degree of fever (100° to 103°) was present in all mild or moderate cases. In severely ill cases the temperature frequently was more elevated (103° to 105°). All patients who came under observation early in their illness, on the first to the third day, had rather low temperature elevations regardless of the later serious proportions which the disease assumed. More than half of the patients exhibited a striking relative bradycardia. Over three-fourths of the patients failed to have rapid respiration at the time of their appearance at the hospital generally on the fourth or fifth day.

The *chest findings* on admission even as late as the fourth or fifth day often were insignificant and generally lagged behind roentgenologic changes. Often slight suppression in breath sounds was the only presenting feature of the chest examination. Moist or sibilant râles were elicited ordinarily at the end of inspiration in many of the patients entering observation when their disease was more established. As the disease increased in severity for a variable number of days more chest findings appeared. Abundant moist type râles were present in almost every case; if not at the onset, they appeared as the disease reached its maximal proportions. Increasing impairment on percussion and suppression of breath sounds appeared later in many cases. Tubular or bronchial breathing occurred infrequently, generally being limited to the severely ill patients.

The *fever* showed certain definite characteristics in almost every case. The temperature varied widely in 24-hour periods and as the disease reached the maximal stage, the lowest temperatures each day approached the normal level. Very few cases showed high plateaus of fever. In most cases the admission temperature was quite elevated except in patients who entered early in the course of the disease. Fever was out of proportion to the general appearance and presenting signs. In frequent instances before the development of physical signs, blood cultures, Widal tests, and other blood agglutinations were obtained because of the marked disproportion between the relatively high fever and low pulse. With the progress of chest developments and as the temperature began to fluctuate to lower limits the pulse became proportionately faster. The duration of fever varied in the 3 groups of cases: in mild cases 10.6 days, in moderate cases 16.2 days and in severe cases 29 days.

Generally speaking, the *chest findings* of râles and dullness became maximal as the temperature began to show lower fluctuations. Remissions of severe proportions occurred in about one-half of the very ill patients. There were no complicating infections observed either in the upper or lower respiratory tract.

While the patients remained under observation in the *postfebrile period*, the physical signs in the chest tended to persist for relatively long periods. Bronchiolar congestion with moist râles was the feature. Actual bronchial breathing, dullness, or on the other hand absence of chest findings, were encountered only in a small number of patients. During this stage of the disease there was little malaise or anorexia corresponding to that seen in influenza.

Laboratory Data. The *white blood count* in 55% of the cases was below 8000 on admission; higher counts were observed in a small number, in some instances possibly related to the more advanced stage in the evolution of the disease when medical aid was sought. Neutrophil percentages were also within normal range in the early days of the illness. In almost all cases the white blood count trend was initially up and later down to normal. The differential count occasionally showed a moderate left shift.

Sputum typing performed at least twice in most of our cases both by the Neufeld method and by inoculation of mice, seldom revealed pneumococci.

Sputum showed no significant identifiable organisms. Such commensals as non-hemolytic streptococci, *Strep. viridans*, *Micr. catarrhalis*, rarely pneumococci, diphtheroid bacilli and occasionally staphylococci were cultured. In many of the moderately and severely sick patients sputum cultures were repeated at intervals to ascertain the presence of possible secondary pyogenic invaders. The frequency with which reports were returned showing "no growth" or "very few organisms present" deserves comment.

Blood cultures were obtained at least once in each case and were never positive.

Urinalyses showed a transient 1+ or 2+ albuminuria in a relatively small number of the more severely ill patients. Hematuria of varying degree has been observed in a few cases.

In 6 instances electrocardiograms were obtained because of the presence of gallop rhythm. Three patients, all severely ill, showed abnormalities. In 2 instances T-wave abnormalities occurred in Leads II and III. These changes were interpreted as possibly reflecting increased cardiac strain.

One of these individuals, a woman aged 50, had an extensive pulmonary involvement in both lungs as shown by physical examination and Roentgen ray. Dyspnea and cyanosis were marked and the febrile period was very prolonged. A remission occurred 5 weeks following initial subsidence of fever. During both primary and secondary periods of fever the patient was described by different observers as being "almost moribund." Recovery progressed very slowly.

In a second instance, also in an older individual, after dense consolidation had occurred in both lower lobes, and during the height of his illness with high fever and tachycardia, a transient pericardial friction rub was observed. Serial electrocardiograms showed a pro-

longed PR conduction which subsequently returned to normal several weeks after the clearing of all symptoms and signs of his illness except for delayed resolution in both lower lobes.

Pleural effusion was proven to have occurred in 2 instances and the fluid was sterile on culture. In each case the fluid was clear and light amber colored and contained only a few lymphocytes and polymorphonuclear leukocytes. Because of clinical signs suggesting fluid, thoracenteses were performed in 3 other instances but no fluid was obtained.

Roentgen Ray Changes. Excellent descriptions of the variety of Roentgen ray changes which may be found have been published by Kornblum and Reimann,⁸ Kneeland and Smetana,⁷ and by Longcope.⁹ Our cases exhibited the various types of Roentgen ray changes referred to by these authors. In general, the milder cases presented lesser amounts of infiltration than sicker individuals. The type of Roentgen ray change included small patchy densities, fine hazing often involving half of a lung field, a widespread miliary infiltration or a dense area occupying a portion of the lung and corresponding in appearance to "lobar pneumonia." The areas seen in the lung showed a tendency to migrate to new locations on the same side or to the opposite side. In almost one-half of the patients both sides of the chest were ultimately involved. In the initial stages when the infiltration involved the apical region only, differentiation from early tuberculous exudation was impossible. In one patient (Case 2) a pneumothorax was begun before further developments regarding her clinical course and later information relating to contact with an established case of this disease came to light.

In milder cases Roentgen ray densities were transient; in severely ill individuals the appearance of widespread floccular lesions or heavy density persisted for surprisingly long intervals.

The duration of positive Roentgen ray changes showed remarkable parallelism when compared with degree of morbidity.

MINIMUM DURATION OF ROENTGEN RAY CHANGES.

(1)	25	Mild cases	Average 9 days	Limits 3-21 days
(2)	17	Moderate cases	Average 17.3 days	Limits 10-43 days
(3)	10	Severe cases	Average 47 days	Limits 15-90 days

The accompanying table illustrates in a general way the various Roentgen ray features presented by these cases.

ROENTGEN RAY FEATURES.

Bilateral	23
Unilateral migratory	12
Apical infiltration	7
Diffuse miliary or floccular	4
Lobar density	10

Several chest Roentgen rays are presented from 4 cases illustrating some of the roentgenographic features of this disease.

Incubation Period. In accord with other reports the incubation periods noted were from 10 to 26 days in 6 instances where there were definitely known exposures; the average period was 18.7 days. The details of these exposures indicate that the disease is readily transmissible. In one instance a patient (S. S., a psychiatric department nurse) visited her sister (O. S) only once during the latter's hospitalization. Sixteen days later the nurse became ill and eventually was admitted to the hospital where her disease assumed serious proportions.

Source. Thirty-seven of the cases occurred in patients drawn from other than institutional sources, while 10 cases have occurred

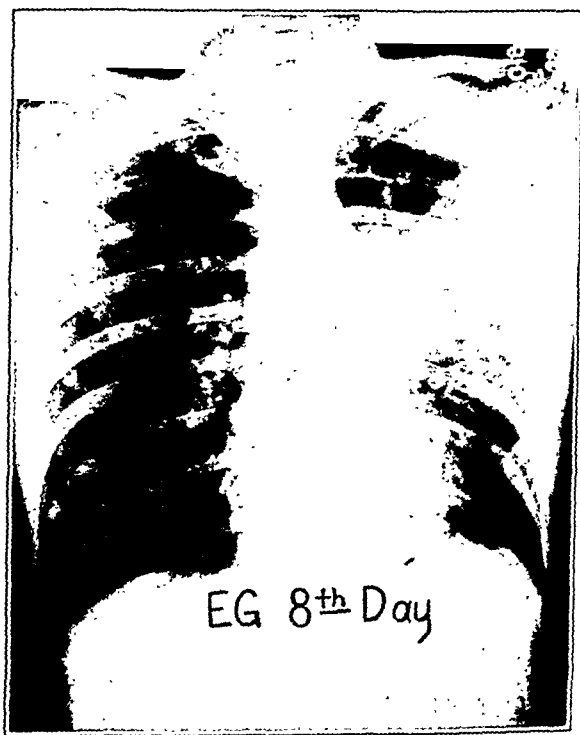


FIG. 1 (Case 1).

among hospital personnel and 5 cases from among patients transferred from the "sick bay" at the River Rouge Naval Service School to this hospital. It is evident that this disease is no longer limited to institutional outbreaks involving younger age groups.

Discussion. This group of cases is presented without any direct evidence that a virus was the causative organism. As has been pointed out above, investigation of the virus agent has been carried out by a number of workers. Prior recovery of a virus from similar cases and the absence of significant findings in sputum or blood



FIG. 2 (Case 1).

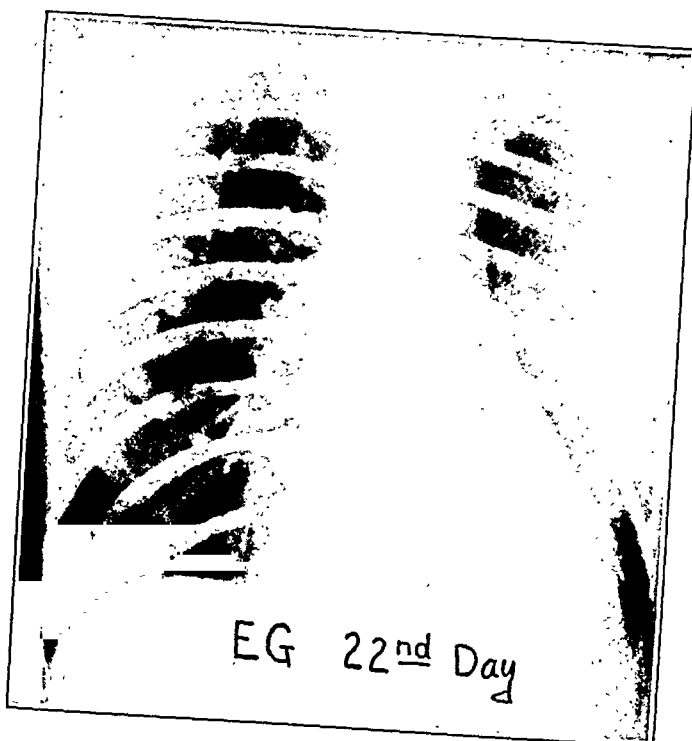


FIG. 3 (Case 1).

favor a non-bacterial etiology. Certain resemblances to other virus diseases in reference to course, length of incubation period and ease of transmission suggest the virus nature of this disease.¹⁴ The term "virus type pneumonia" for this form of respiratory disease appears warranted.⁴

The diagnosis pneumococcus pneumonia²⁰ is receiving wider usage now that more exact bacteriologic analysis has been introduced and it is probable that the designations lobar or bronchopneumonia may be less often applied. These latter names may remain as useful terms in roentgenology and pathology.

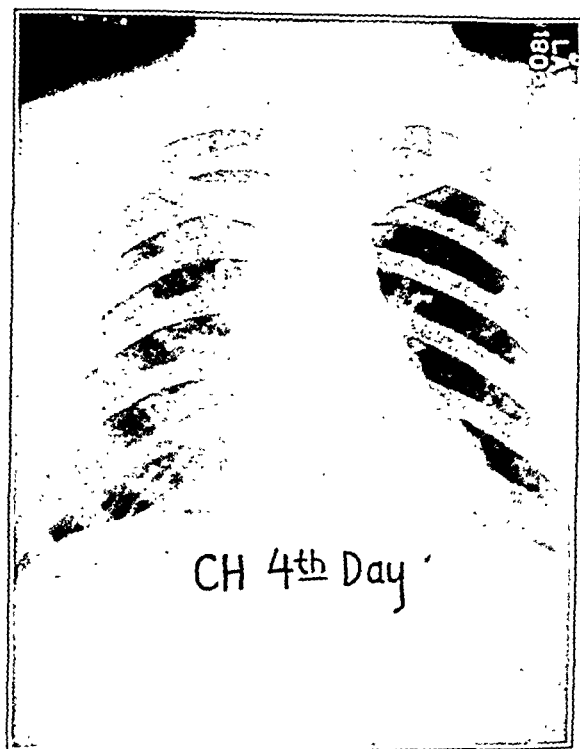


FIG. 4 (Case 2).

Prompt recognition of this disease is important in order to prevent institution of possibly harmful therapeutic measures, or their continuation when obviously not helpful. In most instances, a positive diagnosis can be made clinically. The history of an insidious onset featured by headache, cough and chilliness with mucopurulent sputum and some aching pain in the chest is characteristic. Temperature and pulse disproportion with fever of considerable degree having a sharply fluctuating course and falling by lysis is also a contributory feature in diagnosis. Generally the aëæ do not dilate:

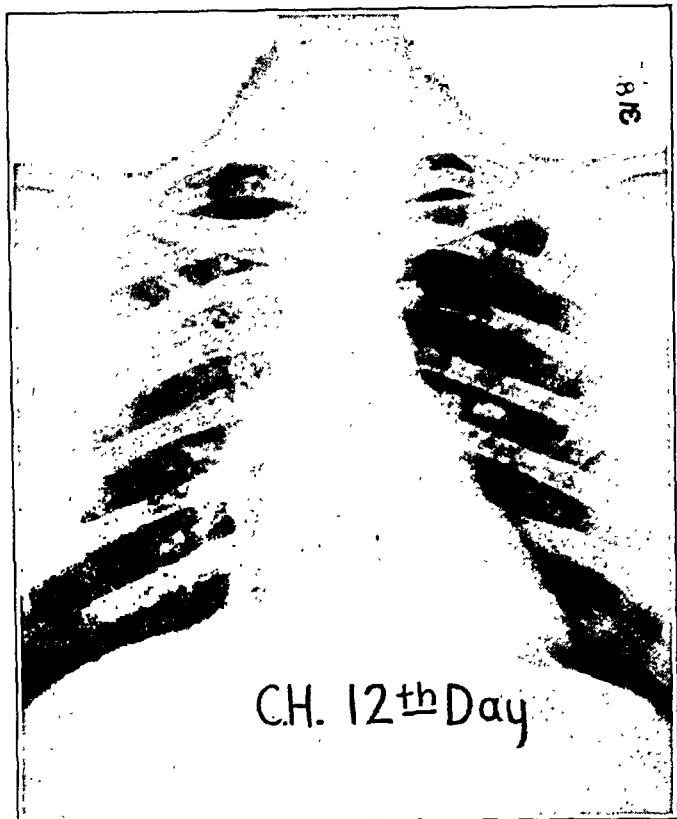


FIG. 5 (Case 2).

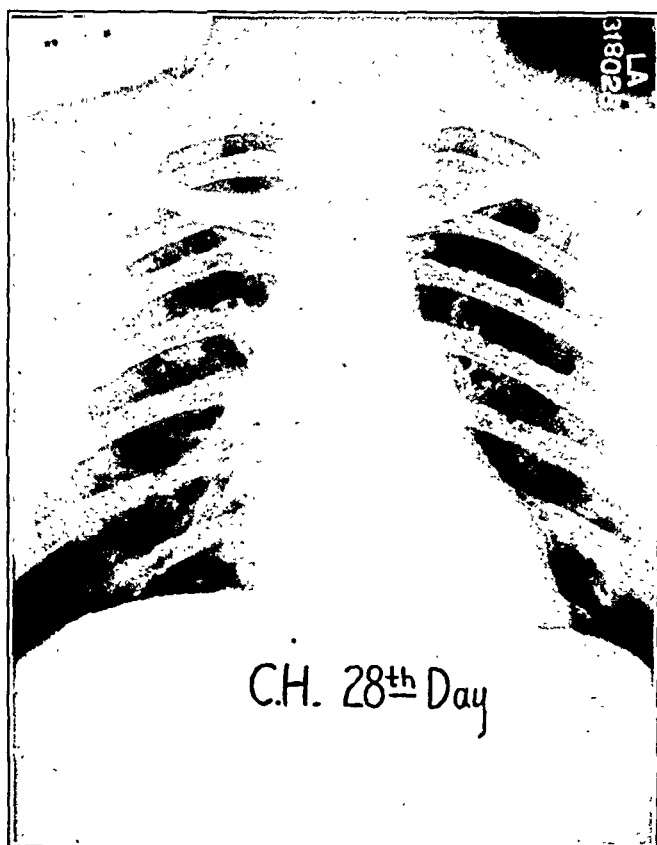


FIG. 6 (Case 2).

there is no cyanosis within the first 4 to 5 days but there may be considerable later. Distention of the abdomen and liver congestion are absent. There is no pleural pain of the type seen in pneumococcus pneumonia; instead there is an aching in the chest which may or may not be influenced by respiration. Even on the third or fourth day chest findings are insignificant in proportion to the degree of fever, generally there are a few râles late in inspiration or suppression of breath sounds. Initial chest roentgenograms are often not abnormal but later as more chest findings appear may reveal infiltration. The sulfonamide drugs are without effect in treatment. In doubtful cases where initially the diagnosis may be in question, a trial of these drugs may further help in establishing the diagnosis. As yet we know of no definite laboratory test that gives positive evidence of the disease except methods designed to recover the virus itself from throat washings, and for best results this probably should be done within the first 3 days of the illness.¹⁹

In regard to treatment, the only measures definitely indicated are symptomatic. Blood transfusions have been given to a number of our severely ill patients but there has been no constant response. Sulfonamide drugs, including sulfapyridine, sulfathiazole, and sulfadiazine, have not shown any indications of value in treatment. Neoarsphenamine has been tried in 3 cases without results sufficiently promising to deserve comment. Oxygen may be administered where dyspnea or cyanosis exist in significant degree, preferably by tent with admixture of intercurrent use of carbon dioxide.

Only 4 deaths have been reported to date. One of these occurred in association with involvement of the central nervous system. The 2 fatalities reported by Longcope occurred in individuals having mitral stenosis. The increasing frequency of the disease and the rather large number of patients in this group that were seriously ill suggest that deaths may become more numerous. It is not probable that deaths will be related to the harmful effects of secondary invaders such as occurred in the influenza pandemic. Longcope has stated that this disease, which has been differentiated from influenza, appears to increase the resistance of the patient to pyogenic organisms.⁹ Our experience supports this statement.

Francis⁵ and other workers have observed a high antibody titer in respect to influenza type A during the third decade of life. All reports of virus type pneumonia have stressed the occurrence of the disease principally in this same age group. In the future it may be found that antibody titers for this virus differ sharply from those of influenza A virus.

The increasing incidence and severity of virus type pneumonia indicate a rising virulence of the etiologic agent. In epidemic or pandemic form the mortality rate would be expected to increase, especially in the older age group. It is probable such deaths would result from failure of the circulation in the presence of widespread



FIG. 7 (Case 3).

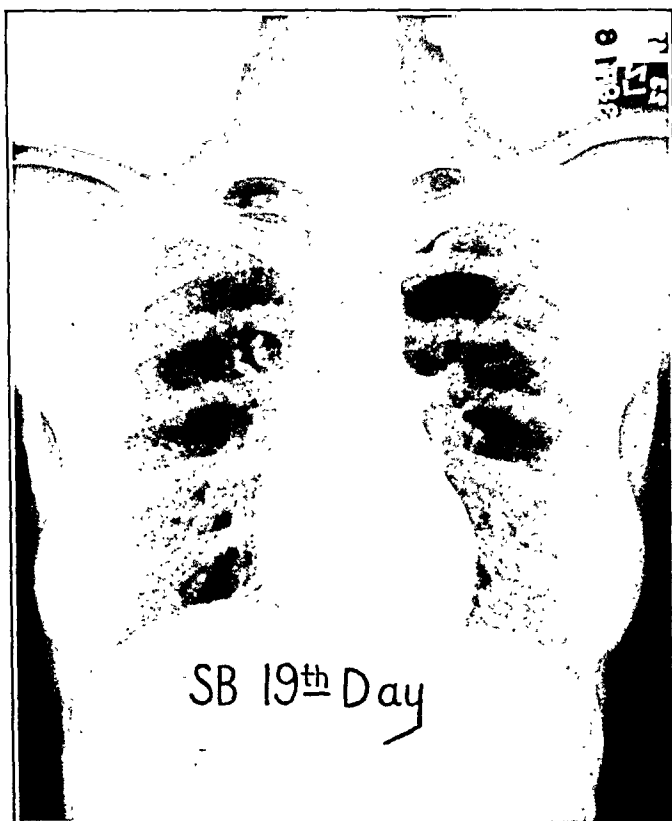


FIG. 8 (Case 3).

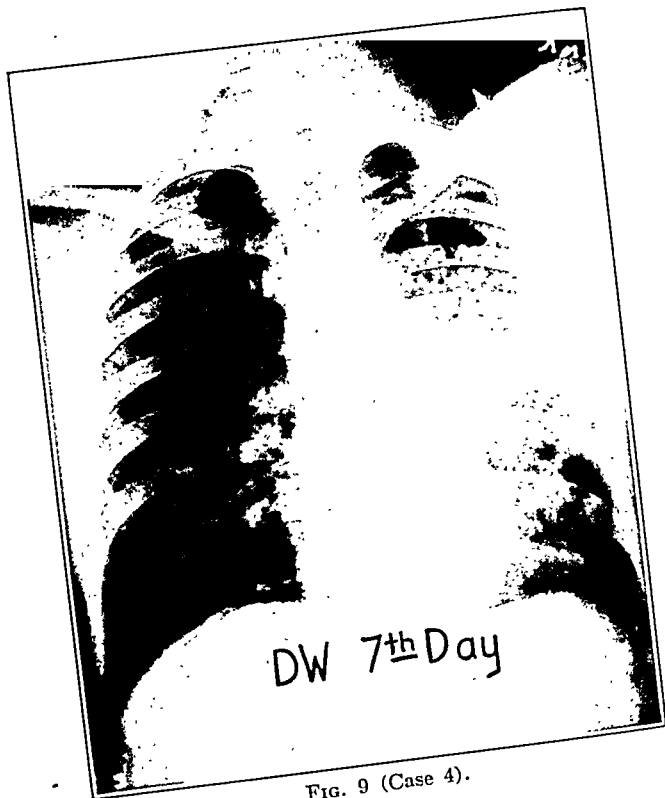


FIG. 9 (Case 4).

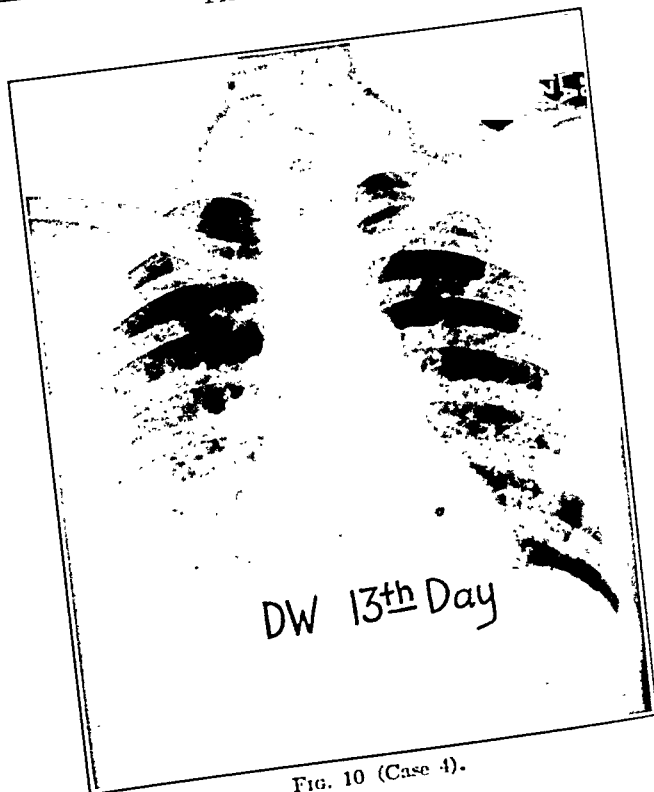


FIG. 10 (Case 4).

pulmonary changes, which changes have been encountered already in some patients.

TABLE 1.—DIFFERENTIATING CRITERIA IN THREE TYPES OF PNEUMONIA.

	Pneumococcus.	Virus type.	Influenza.
Incubation	1-2 days	2-3 weeks	1-4 days
Onset	Abrupt	Insidious	Abrupt
Symptoms	Chill	Chilliness	Repeated chills
	Pleural pain	Headache	Aching
Cough	Loose	Dry	Loose
Sputum	Rusty	Mucoid	Bloody
Appearance	Toxic	Not toxic	Markedly toxic
Dilatation alæ	+	0	+
Herpes	Frequent	Rare	Infrequent
Heart rate	Rapid	Slow (50%)	Slow at times
Respiratory rate	Elevated	Normal	Normal
Distention	Frequent	None	Variable
Fever	Maintained	Hectic	Remittent
Chest findings:			
Impairment	Early	None or late	Infrequent
Tubular breathing	Frequent	Rare and late	Infrequent
Râles	Variable	Moist (end of inspiration)	Fine crackling
Sputum	Pneumococci	Occas. higher type	B. influenza often
	Direct typing	Pneu. culture	Streptococcus
WBC	High	Normal	Low
Roentgen ray	Dense consolidation	Often bilateral lobular (lobar and miliary at times)	Variable diffuse Lobular
Treatment	Response to chemotherapy	No response	For secondary invaders
Pyogenic complications	Not frequent	None	Very frequent

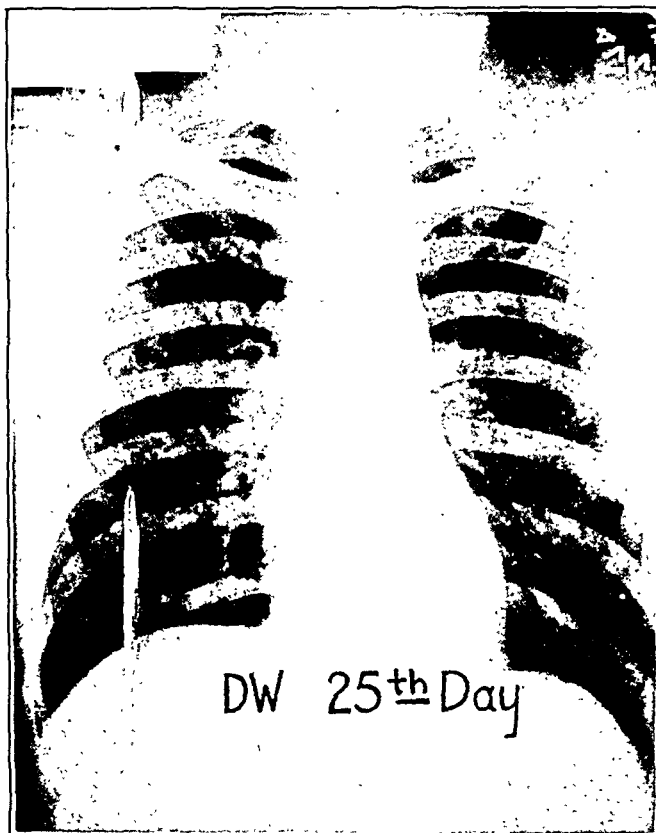


FIG. 11 (Case 4).

CASE 1. E. G., nurse, aged 30, 14 days after exposure, began having symptoms of headaches, cough and fever and 6 days later entered the hospital. Temperature 104.2°. White blood count 5100. Râles were audible in left upper and there was slight impairment on percussion. Infiltration in left upper appears on the eighth day. Involvement in right lower showed on the twelfth day. Ten days later no Roentgen ray shadow remains on the right. Pneumothorax which had been begun after an initial diagnosis of acute exudative tuberculosis was discontinued. Recovery occurred.

CASE 2. C. H., staff physician, aged 27, 23 days after exposure was admitted in the second day of headache, dry cough, and malaise. On the fourth day of his illness examination and chest Roentgen ray were essentially negative. White blood count 6800. Temperature was 101°. Soon after the appearance of râles in the right upper a chest film on the twelfth day showed parenchymatous infiltration in the right upper. After other films showed rapid clearing, a final Roentgen ray on the twenty-eighth day was clear.

CASE 3. S. B., 21-year-old girl, was admitted on eighth day of illness consisting principally of cough, fever, malaise and aching in both sides of the chest. Temperature on admission 102.4°. White blood count 7850. Chest Roentgen ray on admission (eighth day) showed dense consolidation in both lower lung areas. Physical examination revealed mainly dullness and râles bilaterally in lowers. Another film on the nineteenth day showed a moderate amount of infiltration remaining.

CASE 4. D. W., 28-year-old Naval ensign, entered hospital on seventh day with cough, severe sweats and fever. White blood count 18,050. Temperature 99.2°. Chest examination revealed râles in left upper. Chest Roentgen ray showed consolidation in the mid-portion of the left lung. Six days later a film showed fine nodular appearance simulating hematogenous spread of tuberculosis. On the twenty-fifth day the lung fields were almost clear.

Summary. 1. Virus-type pneumonia presents specific clinical features permitting diagnosis by positive findings. Diagnosis by exclusion alone is seldom necessary.

2. Chemotherapy with the sulfonamide group of drugs is not indicated in this disease. Recognition of this disease may avoid needless and possibly dangerous therapeutic efforts.

3. The initial roentgenographic appearance may closely simulate acute exudative tuberculosis. Progress roentgenographic study may be necessary for differentiation.

4. There is evidence that this disease is now showing an increasing incidence. This fact is not alone explained by familiarity with the clinical concept.

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SULFADIAZINE IN PNEUMONIA.

TREATMENT IN 239 CASES.*

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SULFADIAZINE (2-sulfanilamido-pyrimidine) is the latest member of the sulfonamide group to be given extensive clinical trial in the treatment of pneumonia. Sulfapyridine was the first of these drugs to show a striking therapeutic effect in pneumonia, but from the start the almost universal occurrence of nausea following sulfapyridine militated against its use. Sulfathiazole was the next sulfonamide drug to have extensive use in pneumonia, and while there was less nausea and vomiting following its administration, there were other evidences of greater toxicity and, in addition, the clinical

* This investigation has been conducted under a grant of the Josiah Macy, Jr. Foundation. The sulfadiazine was supplied by Lederle Laboratories, Inc.

response was not quite as certain as with sulfapyridine. Consequently, many physicians felt more secure in continuing to use sulfapyridine in the treatment of pneumonia in spite of the bothersome gastric symptoms which are produced. The data that are accumulating from the trial of sulfadiazine would indicate that: 1, it has a protective value at least equivalent to that of sulfapyridine; 2, it causes little or no nausea and vomiting; and 3, there is a low incidence of other toxic reactions.

In August, 1940, Roblin, Williams, Winnek, and English⁹ reported upon the synthesis and chemistry of sulfadiazine. In December, 1940, Feinstone and his associates² described their experimental studies on the toxicity, absorption, and chemotherapeutic activity of this new sulfonamide drug. Their experiments in animals indicated that: 1, the blood levels of sulfadiazine were higher than those of the other sulfonamide drugs because of differences in absorption and excretion; 2, the degree of acetylation of sulfadiazine was less than of sulfapyridine; 3, the acute and chronic toxicity was lower than that of sulfapyridine and sulfathiazole; 4, sulfadiazine had a high therapeutic activity against pneumococcal, streptococcal, staphylococcal, and Friedländer's bacillus infections in mice.

These experimental advantages have been borne out by clinical trial. Plummer and Ensworth,⁶ Reinhold, Flippin, Schwartz, and Domm,⁸ Peterson, Strauss, Taylor, and Finland,⁵ and Sadusk and Tredway¹⁰ have reported findings that indicate: 1, with a given dosage, because of differences in absorption and excretion, higher blood levels are obtained with sulfadiazine than with sulfapyridine or sulfathiazole; 2, sulfadiazine acetylates to a lower degree than sulfapyridine; 3, the incidence of clinical toxicity is low. Reinhold, Flippin, Schwartz and Domm showed also that sulfadiazine enters the peritoneal, pleural, and cerebrospinal fluids more readily than sulfathiazole. More recently Flippin, Rose, Schwartz and Domm¹ have compared their experience with sulfadiazine in the treatment of 100 cases of pneumonia with a similar experience with sulfathiazole. Their findings showed again higher blood levels of sulfadiazine, and also less acetylation with this drug. In addition, their figures show a slightly lower mortality rate, a slightly more rapid clinical improvement, and a lower incidence of toxic reactions with sulfadiazine than with sulfathiazole. Finland, Strauss and Peterson³ have reported the successful use of sulfadiazine in a number of infections, including pneumonia, with infrequent toxic reactions. Dowling, Hartman, Sugar and Feldman¹ have reported favorably on the use of sulfadiazine in pneumococcic pneumonia.

The present report represents our clinical findings in 239 patients with pneumonia treated with sulfadiazine at Bellevue Hospital during the winter of 1940-41. These cases were part of an alternate series being carried out in order to ascertain the relative efficacy of sulfonamide drugs alone and sulfonamide drugs combined with

serum in the treatment of pneumonia. However, since this study has already been reported⁷ and because it reveals no appreciable difference* between the fatality rate in the chemotherapy-alone cases and the chemotherapy-and-serum group, such a division in this report seems unnecessary. Only cases of pneumococcus pneumonia are included. The majority of the cases fall into the classification of lobar pneumonia, but a few might be called bronchopneumonia. The sulfadiazine was administered orally in most of the cases and the usual dosage was 2 gm. initially and then 1 gm. every 4 hours. All cases had routine sputum typing and one or more blood cultures. Frequent determinations of sulfadiazine level in the blood were made, as well as blood counts, urinalyses and Roentgen rays. An initial blood non-protein nitrogen determination was obtained in each case.

Effect on Fatality Rate. Table 1 shows the cases distributed according to pneumococcal type and lists the deaths in the total group as well as in the bacteremic group. In the total series of 239 cases, there were 26 deaths (a fatality rate of 10.9%). Eight of the 26 deaths occurred in less than 24 hours after treatment was commenced, and with these excluded there remained 231 cases with 18 deaths (a mortality of 7.8%). Of the 239 cases, 42 (17.4%) were bacteremic, and of these, 13 (30.9%) died. The fatal cases were distributed quite evenly through the different types. While there were 33 Type III cases in the series, there were only 3 fatalities (9.1%). The most striking record was obtained in Type II pneumonia. Forty-two patients were of this type, and there were only 3 deaths, 2 of which occurred less than 24 hours after treatment was started. Thirteen of the 42 Type II cases showed bacteremia and all but 2 of these recovered; 1 of these 2 was a 24-hour fatality. The Type I group contained 44 cases with 4 deaths (1 of which was a 24-hour death) and 10 bacteremias with 3 deaths (1 of which was a 24-hour death). The temperature chart of our most remarkable patient is shown in Figure 1.

* Of the 113 patients who fell into the serum-plus-sulfadiazine group, 67 actually received serum, the rest having marked improvement by the time the typing was completed. Of these 67 cases, 16 were Type I; 17, Type II; 9, Type III; 5, Type IV; 2, Type V; 6, Type VII; 2, Type VIII; and 10 were higher types.

The results in the present series of 239 cases show a moderate difference in fatality rates in favor of sulfadiazine-plus-serum treatment, 9 of 113 patients (7.9%, or excluding 24-hour deaths, 5.5%) in this group having died. Of the 126 sulfadiazine-only cases, 17 died (13.5%, or excluding 24-hour deaths, 9.9%). In view of the comparatively limited number of sulfadiazine cases, however, the significant figures in our alternated series study are those obtained by adding the present cases (less 51 cases included previously) to those already reported. This gives the following final figures for our alternated series:

	Cases.	Deaths.
Drug only	403	47 (11.66%)
Drug plus serum	392	48 (12.24%)
Eliminating 24-hour deaths:		
Drug only	393	37 (9.41%)
Drug plus serum	376	32 (8.51%)

TABLE 1.—DISTRIBUTION OF CASES AND BACTEREMIAS AND RESULTS BY TYPES.

Type.	Cases.	Deaths.	24-hr. deaths.	Bactere- mias.	Deaths.	24-hr. deaths.
I	44	4	1	10	3	1
II	42	3	2	12	1	1
III	33	3	0	3	1	0
IV	14	1	1	2	1	1
V	10	1	0	3	0	0
VI	5	1	0	1	1	0
VII	30	3	2	4	2	1
VIII	14	3	0	5	2	0
IX	3	1	0	1	1	0
XI	1	0	0	0	0	0
XII	1	0	0	0	0	0
XIII	2	1	0	0	0	0
XIV	6	1	0	0	0	0
XV	4	1	0	0	0	0
XVI	1	0	0	0	0	0
XVII	3	0	0	0	0	0
XVIII	2	0	0	0	0	0
XIX	2	0	0	0	0	0
XX	5	0	0	0	0	0
XXI	1	0	0	0	0	0
XXII	4	1	1	1	1	1
XXIII	1	0	0	0	0	0
XXV	2	0	0	0	0	0
XXIX	4	0	0	0	0	0
XXXIII	5	2	1	0	0	0
Total	239	26 (10.9%)	8	42	13 (30.9%)	5
Excluding 24-hr. deaths	231	18 (7.8%)	..	37	8 (21.6%)	

E. S.: A married woman of 27 was admitted to Bellevue Hospital with a history of cough and pain in the left chest for 2 days, and expectoration of bloody sputum for 1 day. She was 7 months' pregnant. Signs of consolidation were present over the left upper lobe. The sputum yielded Type I pneumococcus. The blood culture showed innumerable colonies of the same organism. The leukocyte count was 11,600 per c.mm. Sulfadiazine therapy was started at once and she improved rapidly, but on the fifth day of illness she went into labor and delivered a 2-pound 3-ounce baby, who lived for 22 hours. Her temperature, after having been normal for 2 days, began to rise on the seventh day of illness. (See Fig. 1.) She developed a leukocytosis of 40,000 per c.mm. and signs of fluid at the left base and a chest tap on the ninth day yielded 12 cc. of a thin, cloudy fluid, which was positive for Type I pneumococci on culture. Signs of fluid persisted but no fluid was secured by thoracentesis on the eleventh day. In view of her subsequent excellent progress and regression of physical and Roentgen ray signs no further chest taps were attempted and she was discharged in good condition on the thirty-second hospital day after an uneventful convalescence.

Cases Treated Early Compared With Those Treated Late. Division of the cases according to when sulfadiazine therapy was commenced is made in Table 2. Two groups are shown: 1, early (treatment started during the first 3 days); 2, late or uncertain (treatment commenced on the fourth day or later, or duration of illness not ascertainable but usually of considerable length). Of the 108 patients who were treated early, only 7 died (6.5%) (1 24-

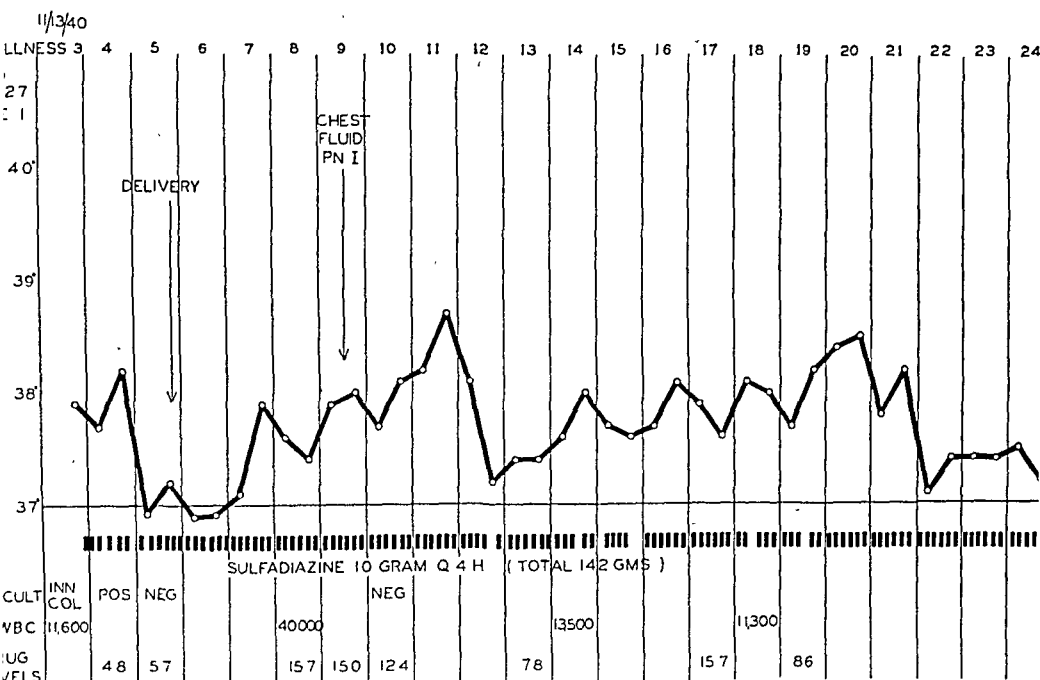


FIG. 1.—Data of patient E. S. with pneumonia, positive blood and pleural fluid cultures, and pregnancy.

hour death is excluded). The late or uncertain cases showed a fatality rate of 8.9% (7 24-hour deaths excluded).

TABLE 2.—DISTRIBUTION AND RESULTS ACCORDING TO DURATION OF ILLNESS BEFORE ADMISSION TO HOSPITAL.*

	Cases.	Deaths.	Fatality rate (%).
Early (first 3 days)	108	7	6.5
Late or uncertain	123	11	9.0

* 24-hour deaths not included.

Relation of Age of Patients to Outcome. While the mortality of 7.8% in 231 cases of pneumonia (excluding 24-hour deaths) treated with sulfadiazine is highly creditable, the results are more remarkable when cases are distributed by the age of the patient (Table 3). Among the 27 patients under 30 years of age, there were no deaths. In the 30 to 50 years group, 86 cases occurred with but 1 death (1.2%). Thus in 113 cases under 50 years of age, there was only 1 death or a fatality rate of 0.89% (24-hour deaths excluded). In the group over 50 years of age there were 118 patients, with 17 deaths (14.4%), excluding 24-hour deaths.

TABLE 3.—DISTRIBUTION OF CASES AND RESULTS BY AGE.

	Cases.	Deaths.	Fatality rate (%).
Under 30	27	0	0
30 to 50	86	1	1.2
50 and over	118	17	14.4
Total	231	18	7.7

* 24-hour deaths not included.

Complications. The complications which occurred in this sulfadiazine-treated series are listed in Table 4, and they have about the same incidence as a larger series of pneumonias treated with sulfonamide drugs reported from Bellevue Hospital,⁷ except that in the present series there are no cases of lung abscess. Empyema has an incidence of 3.3% and endocarditis an incidence of 1.2%. Of the 8 empyemas, 1 was a simple pleural effusion when tapped during life, but at postmortem cloudy infected fluid was found; 2 were small collections of fluid which were discovered only on postmortem examination. Of the 5 empyema patients who lived, 2 recovered after thoracotomy, 1 after thoracenteses (see Fig. 1), and 2 signed out of the hospital before thoracotomy could be done. It is reasonable to assume that if sulfonamide therapy is started early in the infection the incidence of deaths from serious complications can be reduced to a low figure. The 3 endocarditis cases were admitted late in the disease, 1 having been sick for 7 days and the other 2 for an indefinite period.

TABLE 4.—COMPLICATIONS (239 CASES).

	Cases.	Deaths.
Empyema	8	3
Otitis media	5	0
Pleural effusion	5	0
Pneumococcus endocarditis	2	2
Meningitis and empyema	1	1
Pneumococcus endocarditis and empyema	1	1
Otitis media and pleural effusion	2	1
Pericardial effusion	1	1

Toxic Reactions. In spite of the fact that the blood levels (usually 7 to 9 mg. per 100 cc.) during sulfadiazine therapy were higher than those obtained with either sulfapyridine or sulfathiazole, the incidence of toxic reactions was lower (Table 5). Of the 239 total

TABLE 5.—TOXIC REACTIONS (239 CASES).

	Cases.
Nausea and vomiting:	
Before and during treatment	2
Only during treatment	3
Leukopenia	4
Anemia	1
Drug rash and fever	4
Drug fever	2
Microscopic hematuria	4
Renal colic and gross hematuria*	1
Temporary partial deafness	1

* Since this paper was written, further experience with a larger number of cases has shown that renal toxic reactions occur in about 5% of cases.

cases, only 5 vomited and 2 of these had vomited before admission as well as afterwards. Leukopenia occurred in 4 patients; it was of moderate degree in each case and disappeared when the drug was discontinued. There were no instances of agranulocytosis. Anemia, also of moderate severity, was encountered once. There were 4 cases of drug rash with fever, and 2 cases of drug fever. Microscopic

hematuria was found in 4 instances, and renal colic with hematuria occurred in 1 case. One patient had a temporary partial deafness which may have been caused by the drug. In addition, there were several patients who showed temporary mental disturbances during treatment, but nearly all of these patients were chronic alcoholics, and we were unable to decide just what the relative rôles of the alcoholic state, the pneumonia, and the sulfadiazine were; hence we have not listed them. It is likely, however, that the drug was, at least in part, responsible in several cases.

Preëxisting Disease in the Fatal Cases. The incidence of serious preëxisting disease among the 26 patients who died was high. Eight had hypertensive and arteriosclerotic heart disease, and of these, 3 were alcoholics. Two had diabetes mellitus, and 1 of these was in diabetic acidosis. One patient had asthmatic bronchitis, 1 had chronic nephritis and was in uremia on admission, and 1 had acute lymphogenous leukemia. It is our feeling that these preëxisting diseases contributed greatly to the fatal outcome. In addition, 1 patient convalescing from Type III pneumonia developed symptoms and electrocardiographic changes suggestive of acute myocardial infarction and died suddenly.

Summary and Conclusions. 1. Sulfadiazine has been used in the treatment of a group of 239 patients with typed pneumococcus pneumonia.

2. The fatality rate was 10.9% (7.8%, if 24-hour deaths are excluded).

3. There was only 1 death among the 113 patients who were under 51 years of age (1 24-hour death is excluded).

4. The number of complications of the disease was small.

5. The incidence of toxic reactions was low.

6. Sulfadiazine appears to have about the same degree of effectiveness as sulfapyridine and sulfathiazole in the treatment of pneumococcus pneumonia, and at the same time causes fewer toxic reactions.

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THE ABSORPTION, EXCRETION AND DISTRIBUTION OF 2-SULFANILAMIDOPYRAZINE (SULFAPYRAZINE) IN MAN.*

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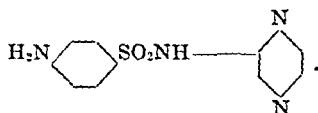
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2-SULFANILAMIDOPYRAZINE ("sulfapyrazine"), the para-isomer of sulfadiazine, was synthesized in 1941 by Ellingson.² Preliminary studies^{3,4} have indicated that its toxicity for man and animals is relatively low, and that its antipneumococcal activity is high.^{3,6} In the present communication, we wish to report studies upon the absorption, excretion and distribution of sulfapyrazine and of sodium sulfapyrazine in man.

Properties of Sulfapyrazine Compounds. The structural formula of sulfapyrazine is



Sulfapyrazine and acetylsulfapyrazine are tasteless white powders, whose solubilities in 100 cc. of water at 37° C. are: sulfapyrazine, 5.2 mg.; acetylsulfapyrazine, 5.6 mg. The pH of sodium sulfapyrazine in 10% aqueous solution is 9.3.²

Plan of Study. *Absorption of Sulfapyrazine.* Blood levels¹ were determined at frequent intervals after single 4 gm. oral doses of sulfapyrazine powder, sulfapyrazine tablets, and sodium sulfapyrazine powder. In addition, many determinations were made on treated patients receiving 1 gm. every 4 or 6 hours. Also, the absorption of sulfapyrazine and sulfadiazine was compared at different times in the same subject.

Convalescent patients on a routine ward diet, with no apparent disease of the gastro-intestinal tract or of the cardiorenal system were used for single dose absorption curves. Their average fluid intake was about 2 liters a day. Powdered drug or crushed tablets were given, before breakfast, suspended in about 300 cc. of water.

* This study was aided by a grant in honor of Craig Yeiser and by a grant from Mead Johnson & Co.

Excretion of Sodium Sulfapyrazine. Four grams of sodium sulfapyrazine monohydrate dissolved in 100 cc. of distilled water were administered intravenously, during 20 to 30 minutes, to normal males, and blood levels determined at frequent intervals. The 24 hour urinary output of 4 of these subjects was collected for 3 or 4 days. In others, the concentration of sulfapyrazine in cerebrospinal fluid obtained from the lumbar sac was compared with that of simultaneously drawn blood, at various times over a 12 hour period. Whenever a local anesthetic was required in obtaining specimens of body fluids, ethyl chloride was used.

Results. **ABSORPTION OF SULFAPYRAZINE.** Four to 8 hours after the oral ingestion of 4 gm. of sulfapyrazine, an average maximum blood level of about 2.7 mg. per 100 cc. is attained. Chart 1 shows that this peak may be reached as early as 2 hours or as late as 12, and that about 1 mg. per 100 cc. is still present in the blood

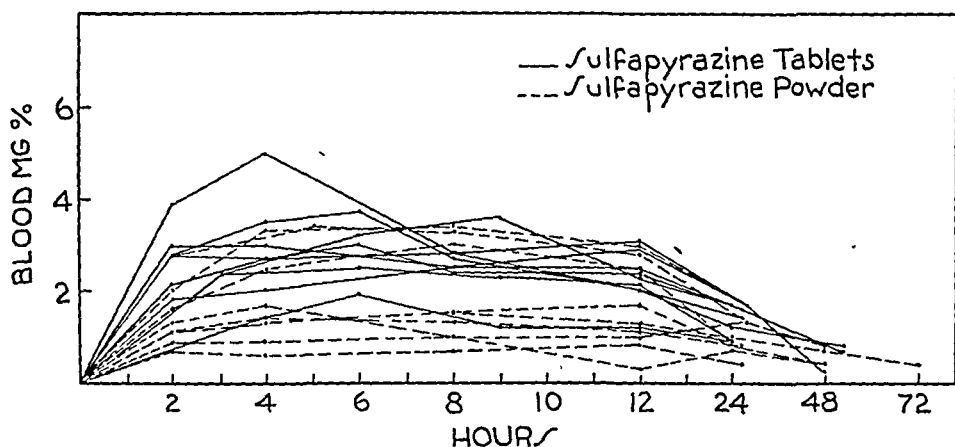


CHART 1.—Blood levels of free sulfapyrazine following a single oral dose of 4 gm
Each curve represents a separate subject.

after 24 hours. Drug given as powder did not appear to be quite as well absorbed as drug incorporated into tablets. No correlation between size of dose and body weight was found through the range of 50 to 75 mg. per kilo.

When the initial dose of 4 gm. is followed by 1 gm. every 4 hours, blood levels of about 6 mg. per 100 cc. free sulfapyrazine and 8 mg. total sulfapyrazine are usually maintained (Table 1).^{*} These are

TABLE 1.—SULFAPYRAZINE LEVELS IN PATIENTS UNDER TREATMENT.

Dosage.	No. of observations.	Highest level recorded in any patient (mg./100 cc.).	Lowest level recorded in any patient (mg./100 cc.).	Median of all levels recorded (mg./100 cc.).
1 gm. every 4 hours:				
Free	67	16.5	2.0	6.5
Total	61	21.2	3.1	8.1
1 gm. every 6 hours:				
Free	73	11.5	0.6	4.7
Total	66	12.9	0.9	5.6

^{*} Blood level determinations in the early sulfapyrazine-treated patients³ were performed in the general clinical laboratory of the hospital by substitute technicians. It is believed that these levels were probably lower than the levels actually attained and are not included in this table.

comparable to the levels maintained by 1 gm. of sulfadiazine every 6 hours.⁵ When the initial 4 gm. dose of sulfapyrazine is followed by 1 gm. every 6 hours, average blood levels of 4 to 5 mg. per 100 cc. are maintained. Similarly the maximum blood level following a single oral dose tends to be lower for sulfapyrazine than for sulfadiazine. Table 2 compares the absorption of the two drugs in the same subject at different times.

TABLE 2.—COMPARISON OF MAXIMUM BLOOD LEVEL ATTAINED BY SULFAPYRAZINE AND SULFADIAZINE IN THE SAME SUBJECT.

Subject.	Free.		Total.	
	Sulfapyrazine (mg./100 cc.).	Sulfadiazine (mg./100 cc.).	Sulfapyrazine (mg./100 cc.).	Sulfadiazine (mg./100 cc.).
M. B.	2.5	3.8	3.2	4.6
Q. W.	3.1	5.6	3.7	6.1
F. B.	3.0	5.5	4.0	6.3
C. H.	2.8	2.8	3.4	3.0

Figures represent the highest blood level recorded after a single oral dose of 4 gm. The interval between the administration of the two drugs was at least 5 days.

Chart 2 depicts the absorption of sodium sulfapyrazine from the gastro-intestinal tract. As is the case with sodium salts of other

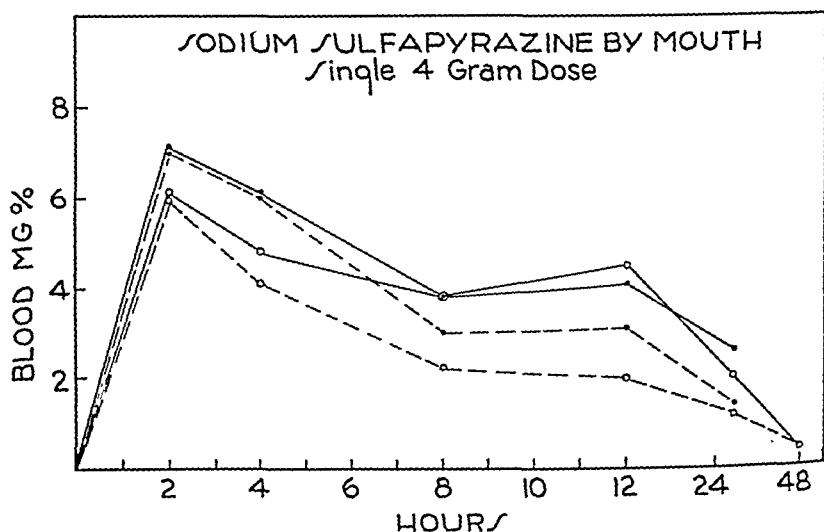


CHART 2.—Blood levels following sodium sulfapyrazine by mouth, in 2 subjects. Dotted lines represent "free" levels; solid lines "total" levels.

sulfonamides, sodium sulfapyrazine is absorbed more rapidly and attains higher blood levels than the acid drug.

BLOOD LEVELS FOLLOWING INTRAVENOUS SODIUM SULFAPYRAZINE. Four grams of sodium sulfapyrazine monohydrate were administered intravenously to 9 subjects and 6 gm. to 1 (Chart 3). Blood levels were determined 4, 8, 12, 24, and 48 hours after the completion of the injection in all individuals, and $\frac{1}{2}$, 1, 2, and 72 hours as well in some.

This compound is excreted rather slowly. At the end of 8 hours, the "free" blood level averaged 6 mg. per 100 cc., and at the end of 12 hours, 3 mg. per 100 cc. Some drug remained in the blood after 24 hours and traces after 48 and 72 hours.

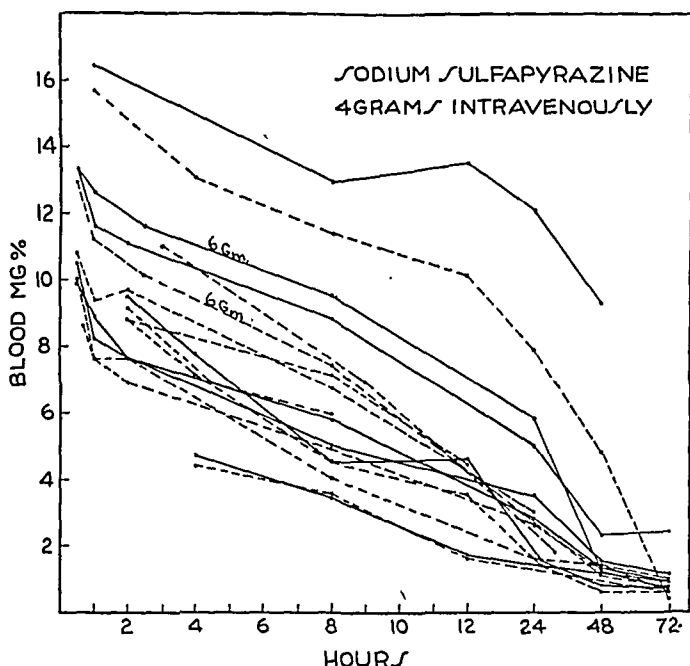


CHART 3.—Blood levels following injection of 4 gm. sodium sulfapyrazine monohydrate (3.44 gm. sulfapyrazine) intravenously. Dotted lines represent "free" sulfapyrazine; solid lines, "total" sulfapyrazine.

RENAL EXCRETION OF SULFAPYRAZINE. Table 3 shows the rate of renal excretion of sulfapyrazine following an intravenous injection of 4 gm. of sodium sulfapyrazine monohydrate. Thirty-five to 50% of the drug is excreted in the first 24 hours. Another 20% to 25% is eliminated in the second 24 hours, and about 5% in the third. The total amount of sulfapyrazine accounted for in the urine was only 70% of that injected. In this respect, the excretion of the drug resembles the excretion of sulfamethylthiazole, as reported by Strauss *et al.*⁷

Subject A. S. was used to compare the excretion of the sodium salts of sulfapyrazine, sulfadiazine and sulfathiazole in the same individual at different times. Sulfathiazole was excreted most rapidly, sulfadiazine less rapidly, and sulfapyrazine most slowly.

No attempt was made to estimate total excretion of the drug by patients receiving it orally. However, many determinations were made on single urine specimens and on 12 or 24 hourly samples. These are summarized on Table 4. The only pertinent fact contained in these data is the great variability of the urinary concentration, which was undoubtedly conditioned by the volume and the

TABLE 3.—RECOVERY OF SULFONAMIDES IN URINE FOLLOWING INTRAVENOUS INJECTION OF 4 GM. OF THE MONOHYDRATE SODIUM SALT.

Subject and age.	Drug.	Period (24 hrs.).	Urine vol. (ml.).	Drug (mg./100 cc.).		% recovered drug conjugated.	Administered drug recovered in urine.	
				Free.	Total.		Gm.	%.
L. H. 18	Sulfapyrazine	First	2200	30.6	58.4	48	1.28	37.3
		Second	2550	14.0	32.8	57	0.84	24.3
		Third	1540	7.2	16.6	57	0.26	7.5
		Fourth	2100	2.9	4.9	41	0.10	2.9
		Total	2.48	72.1
E. A. 24	Sulfapyrazine	First	2560	21.0	55.2	62	1.41	40.8
		Second	2570	8.7	33.9	74	0.87	25.5
		Third	935	10.3	24.0	57	0.22	6.4
		Total	2.50	72.7
A. S. 47	Sulfapyrazine	First	2580	57.0	66.3	14	1.71	49.7
		Second	1160	48.6	64.2	24	0.75	21.8
		Third	1140	3.9	4.7	17	0.01	0.3
		Fourth	1080	4.4	7.7	43	0.01	0.3
		Total	2.48	72.1
A. S.	Sulfadiazine	First	2020	84.1	102.5	18	2.07	60.0
		Second	1700	24.9	45.7	46	0.78	22.7
		Third	1250	6.8	7.7	12	0.10	2.8
		Total	2.95	85.5
A. S.	Sulfathiazole	First	995	200.0	260.3	23	2.60	75.5
		Second	600	12.6	18.0	30	0.11	3.2
		Third	1380	2.5	4.6	46	0.06	1.8
		Fourth	1500	0	0	0
		Total	2.77	80.5

4 gm. sodium sulfapyrazine monohydrate contain 3.44 gm. sulfapyrazine.

TABLE 4.—LEVELS OF SULFAPYRAZINE IN 30 RANDOM URINE SAMPLES OF PATIENTS UNDER TREATMENT, 1 GM. EVERY 4 HOURS.

	Free (mg./100 cc.).	Total (mg./100 cc.).	% conjugated.
Median	51	101	53
Highest	185	300	86
Lowest	8	12	20

hydrogen ion concentration of the sample studied. Both sulfapyrazine and acetylsulfapyrazine are many times more soluble in alkaline than in acid urine (Table 5). As is the case with sulfadiazine, the solubility of the acetyl derivative exceeds that of the "free" compound.*

TABLE 5.—SOLUBILITY OF SULFAPYRAZINE AND OF ACETYSULFAPYRAZINE IN BUFFERED URINE.

Final pH.	Sulfapyrazine (mg./100 cc.).	Acetylsulfapyrazine (mg./100 cc.).
4.5	5.1	5.9
5.0	4.9	5.7
5.5	4.0	8.2
5.8	6.0	13.3
6.3	7.7	25.2
6.7	14.2	77.2
7.1	32.6	127.2
7.4	59.1	136.0

* These studies were carried out by Mr. Robert E. Eakin

SULFAPYRAZINE IN CEREBROSPINAL FLUID. Simultaneous blood and spinal fluid levels were determined at various intervals in 4 subjects given sodium sulfapyrazine intravenously. Table 6

TABLE 6.—SIMULTANEOUS LEVELS IN BLOOD AND CEREBROSPINAL FLUID IN PATIENTS RECEIVING 4 GM. SODIUM SULFAPYRAZINE INTRAVENOUSLY.

	Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).		%	Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).		%
	Free.	Total.	Free.	Total.		Free.	Total.	Free.	Total.	
	2 hours.					4 hours.				
L. T.	8.8	..	0.5	..	5.6					
P. B.	13.0	..	2.2	..	16.9
G. B.	4.2	4.7	1.2	1.1	25.3
E. H.	11.0	..	2.1	2.2	19.0					
	8 hours.					12 hours.				
L. T.	7.1	..	1.6	..	25.3	4.2	..	2.1	..	50.0
P. B.	11.4	12.9	3.7	4.4	34.1	10.1	13.5	5.1	6.4	47.4
G. B.	3.5	3.4	1.8	2.0	53.3	1.6	1.7	1.0	1.2	64.2
E. H.	6.7	7.0	3.5	4.1	52.2					

"%" indicates percentage of "free" blood level represented by spinal fluid level.

shows that the sulfapyrazine in the spinal fluid increased gradually until, at the end of 12 hours, its level was 50% to 60% that of the blood level. This ratio is maintained in patients under continuous treatment (Table 7); these patients were free of infection of the central nervous system.

TABLE 7.—SIMULTANEOUS BLOOD AND CEREBROSPINAL FLUID LEVELS IN PATIENTS RECEIVING 1 GM. SULFAPYRAZINE EVERY 4 HOURS.

Patient.	Hours after last dose.	Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).		%	
		Free.	Total.	Free.	Total.	Free.	Total.
C. C.	2.5	2.3	..	1.4	..	60.9	
B. B.	3.0	6.8	..	3.1	..	45.6	
M. P.	3.0	3.1	..	1.1	..	33.4	
W. B.	2.0	10.4	15.3	7.0	7.1	67.3	46.4
E. F.	2.0	8.9	10.7	4.9	5.0	55.0	49.9
J. F.	2.0	12.7	15.9	10.2	10.6	80.3	66.7

"%" indicates percentage of blood level represented by spinal fluid level.

SULFAPYRAZINE IN BODY FLUIDS. Sulfapyrazine reaches concentrations in the pleural and peritoneal cavities approaching and occasionally exceeding that in the blood. A similar observation was made on two samples of synovial fluid, and one specimen of fluid from the anterior chamber of the eye. Smaller proportions of the drug appeared in milk. These data are presented in Table 8.

DISTRIBUTION OF SULFAPYRAZINE BETWEEN PLASMA AND RED BLOOD CELLS. In the blood of treated patients, the concentration of sulfapyrazine in the plasma is approximately double that in the

TABLE 8.—SIMULTANEOUS SULFAPYRAZINE LEVELS IN BLOOD AND VARIOUS BODY FLUIDS.

Patient.	Body fluid.	Dosage, gm.	Hours after dose.	Blood (mg./100 cc.).		Body fluid (mg./100 cc.).		%.	
				Free.	Total.	Free.	Total.	Free.	Total.
N. G.	Pleural	4	6	2.3	3.1	3.2	3.5	141	113
H. G.	Pleural	4	7	3.6	7.3	1.9	4.4	53	60
S. S.	Pleural	4	6	5.9	...	2.3	...	39	...
J. F.	Pleural	4	2½	4.1	4.6	3.5	4.0	85	86
E. C.	Pleural	4	6	3.6	4.4	2.4	3.9	66	88
E. B.	Pleural	1q. 4th hr.	3½	14.8	15.6	16.3	18.6	111	118
Q. W.	Pleural	4	8	3.4	4.4	2.4	2.6	72	59
G. F.	Ascitic	4	5	3.1	3.6	4.0	4.3	129	119
G. B.	Ascitic	4	7	2.0	3.4	2.4	2.7	120	79
J. C.	Joint	4	5½	4.0	5.4	7.3	7.9	182	144
P. W.	Joint	4	..	7.4	8.4	7.2	6.7	97	79
M. M.	* Anterior chamber of eye	4	6	2.9	3.8	1.8	3.0	62	80
E. M.	Milk	4	4	3.1	3.7	1.1	..	34	...
M. H.	Milk	4	4	6.4	..	1.1	..	17	...
C. B.	Milk	4	4	6.0	..	1.1	..	18	...
S. S.	Milk	4	4	2.9	3.0	1.1	1.1	37	35
S. S.	Milk	4	8	2.2	3.1	1.0	1.3	45	42
W. B.	Saliva	1q. 4th hr.	2	10.4	15.3	3.5	..	33	...
E. O.	Saliva	1q. 4th hr.	2	2.3	2.7	1.2	1.2	52	44

"%" indicates percentage of blood level represented by body fluid level.

* Procaine was used as a local anesthetic.

red blood cells (Table 9). In this respect, the drug resembles sulfathiazole and sulfadiazine, but differs from sulfapyridine and sulfanilamide,⁷ which are distributed more uniformly.

TABLE 9.—DISTRIBUTION OF "FREE" SULFAPYRAZINE BETWEEN PLASMA AND RED BLOOD CELLS.

Patient.	Whole blood (mg./100 cc.).	Plasma (P). (mg./100 cc.).	R.B.C. (C). (mg./100 cc.).	P/C.	Hematocrit.
W. B.	5.6	8.3	3.1	2.7	41.5
R. E.	5.9	8.4	4.1	2.0	50.0
W. G.	7.8	10.0	4.4	2.3	...
W. G.	8.7	11.1	5.0	2.2	...
C. W.	7.4	9.6	5.1	1.9	...
E. B.	14.6	18.5	8.5	2.2	...
E. B.	14.8	19.4	9.8	2.0	...
O. B.	2.0	2.5	1.8	1.4	...
J. K.	7.3	10.1	4.2	2.4	...

CONJUGATION OF SULFAPYRAZINE. Following single doses, oral or intravenous, the amount of combined sulfapyrazine in the blood never exceeded 25%, though in patients under treatment, the proportion of combined drug was somewhat higher. The median acetylation is about 30% with extremes of 5% and 78%. In urine the conjugated drug usually exceeds 50% of the total drug.

Discussion. The behavior of sulfapyrazine in the human body closely resembles that of its isomer sulfadiazine. It is absorbed rather slowly from the gastro-intestinal tract, and is excreted more slowly by the kidney than are sulfathiazole and sulfapyridine. It seems likely that as glomerular filtrate containing sulfapyrazine passes down the renal tubules, appreciable amounts of the drug are reabsorbed.

Orally administered sulfapyrazine yields lower blood levels on a given dosage schedule than does sulfadiazine. However, the milligram for milligram antipneumococcal activity of sulfapyrazine, as measured by *in vitro* and by mouse curative tests, is considerably greater than that of sulfadiazine.⁶ The effective sulfapyrazine blood level, therefore, may be lower than the effective sulfadiazine level.

The danger of damage to kidneys by crystals of poorly soluble sulfonamides like sulfapyrazine and sulfadiazine is just as great with the non-acetylated as with the acetylated form. For, in contradistinction to the other sulfonamides in common use, the conjugated forms of these two drugs are just as soluble as the free forms, at any given pH. Since, however, the solubility of both forms rises sharply with increasing alkalinity, careful attention to the maintenance of alkaline urine should, in clinical practice, keep renal complications at a minimum. It is interesting that in dogs, renal calculi containing 75% "free" sulfapyrazine by weight but no conjugated drug are formed in animals kept on large doses for 2 months.⁴

Summary. In a study of the absorption, excretion and distribution of sulfapyrazine in the human body it was found that:

1. The drug is absorbed rather slowly from the gastro-intestinal tract.

2. It is excreted more slowly by the kidney than is sulfadiazine, sulfapyridine, or sulfathiazole.

3. Acetylsulfapyrazine is more soluble in water or urine than sulfapyrazine. Both compounds are many times more soluble in alkaline than in acid media.

4. Sulfapyrazine enters the cerebrospinal fluid slowly, reaching concentrations of about 50% of that of the blood 12 hours after an intravenous injection.

5. Concentrations of the drug in most body fluids approach or exceed the concentrations in the blood; very little sulfapyrazine appears in milk. However, its concentration in the blood plasma is approximately double that in the red blood cells.

We are indebted to Mr. Walter Pritz, Jr., and to Mr. Richard Goldsmith for aid in carrying out the chemical determinations.

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THE EFFECT OF SULFANILAMIDE ON THE EXPERIMENTALLY DAMAGED LIVER.

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THE clinical use of sulfanilamide has been followed in some cases by the development of jaundice. In the majority of instances the jaundice has been hemolytic; in the remainder (about 0.6% of patients who have been treated with sulfanilamide¹³) it has been ascribed to hepatitis.^{1,2,3,6,7,13,17,20} Experimentally, the administration of sulfanilamide to rats has not resulted in damage to the hepatic cells that was detectable by ordinary staining procedures.¹⁵ In an attempt to explain why among some patients receiving the drug hepatitis develops and among others it does not, an attractive hypothesis was advanced by Bannick and his associates.¹ They maintained that the reason for its development among some patients was that their livers had been damaged prior to the administration of sulfanilamide and the drug caused the preëxisting hepatic damage to progress to a stage from which regeneration was impossible.

In order to test the foregoing hypothesis experimentally, four different experiments were planned, each devised to determine the effect of sulfanilamide on the already damaged liver or on the liver predisposed to damage by a recognized procedure. Accordingly, sulfanilamide was administered to: 1, a group of animals in which hepatitis had been induced by means of carbon tetrachloride; 2, a group in which hepatitis was being induced by means of carbon tetrachloride; 3, a group receiving alcohol; and, 4, a group in which obstructive jaundice had been induced by ligation of the common duct.

Procedure. Adult male albino rats of an inbred Wistar strain having an average body weight of 308 ± 54 gm. were used. The rats were fed a standard commercial stock diet, had access to an ample supply of fresh water and were housed 3 per cage. Those animals given sulfanilamide received it daily by means of stomach tube in the form of a suspension in tap water, or in 20% alcohol in the experiment in which alcohol was administered. The amount of sulfanilamide in all cases was 1 gm. per kilogram of body weight; such a dose has been shown to be toxic.^{10,11,14} The animals given carbon tetrachloride were exposed to its fumes in a specially constructed chamber into which air, passed through a bottle of carbon tetrachloride, was forced to enter. The animals were exposed for a period of 30 minutes daily; one such exposure is sufficient to produce a moderate degree of central necrosis extending to and in some instances involving the midzone of the hepatic lobule. Those animals to which alcohol, with or without sulfanilamide was given, received it daily by means of a stomach

tube; the dose given was 6 cc. of a 20% solution. In those animals in which obstructive jaundice had been induced, the common duct had been triply ligated approximately midway between the hilum of the liver and the entrance of the choledochus into the duodenum.

At regular intervals, animals were exsanguinated under light ether anesthesia; the livers were removed and weighed, and portions were fixed in 10% solution of formaldehyde. Sections were stained with hematoxylin and eosin, Sudan IV, the Mallory-Heidenhain stain for connective tissue and Pap's reticulum stain.

Results. *Effect of Simultaneous Administration of Sulfanilamide and Carbon Tetrachloride.* Twelve animals breathed the fumes of carbon tetrachloride for 30 minutes daily until they were killed for necropsy. Six of them also received daily the given amount of sulfanilamide during the entire period. Necropsy was performed on half of the animals at the end of the first week and on the remainder at the end of the second week of the experiment and sections of the livers were fixed for staining.

Necropsies. The livers of both groups of animals necropsied at the end of the first week were enlarged and had prominent lobular markings. Those of the animals that received both carbon tetrachloride and sulfanilamide were dark brown, almost black; while the livers of the animals receiving only carbon tetrachloride were yellow and "nutmeg" in appearance.

Microscopic examination of the livers of those animals that received both sulfanilamide and carbon tetrachloride revealed that the hepatic cells in the central and in portions of the midzones were enlarged. The cytoplasm of these cells stained a faint pink with hematoxylin-eosin, and was vacuolated. The nuclei were pyknotic but centrally placed. The hepatic cells in the uninvolved portions of the lobules appeared normal. There was little or no cellular infiltration in the lobules, and when present, was confined to a narrow portion of the central zone immediately adjoining the central vein (Fig. 1). The sections stained with Sudan IV revealed that the enlarged cells in the central and midzones contained small and large droplets of fat. There was no connective tissue proliferation or condensation and the reticulum pattern was preserved.

The damage was more extensive in the livers of those animals that received carbon tetrachloride only. In a totally irregular manner, small islands of normal hepatic cells were interspersed between larger groups of damaged cells. The latter were enlarged, vacuolated and the affinity of their cytoplasm for the eosin stain varied. The nuclei of these cells were pyknotic but centrally placed. The largest cells contained little or no staining cytoplasm; in some of these only a few faint threads could be seen between a centrally or eccentrically placed pyknotic nucleus and the periphery of the cell (Fig. 2). Some degree of collapse was present about the central vein and in such areas the hepatic cells were replaced by lymphocytes, histiocytes and a few fibroblasts. In the sections especially stained these areas of collapse contained only a few connective tissue

fibers but there was a moderate amount of condensation of reticulum. In the sections stained with Sudan IV many fat droplets of varying size were present only in those enlarged cells which were vacuolated in the sections stained with hematoxylin-eosin.

At the end of the second week, the gross appearance of the livers of both groups of animals was similar to that at the end of the first week, except that the lobular markings of the livers of those animals that received only carbon tetrachloride were more prominent. Microscopic examination again revealed that the livers of those animals that received both sulfanilamide and carbon tetrachloride were less damaged than the livers of the animals that received carbon tetrachloride only. In the sections of the livers of the former, the hematoxylin-eosin stain revealed that the damage to the hepatic cells was not confined to the central zone of the lobules but also occurred in other zones. The pattern of the damage was less regular than at the end of the first week, this being due to regeneration of some of the cells in the inner zones of the lobules. The damaged cells were enlarged and were either vacuolated or else contained only a few fine granules or threads between an eccentrically placed pyknotic nucleus and the periphery of the cell (Fig. 3). The enlarged vacuolated hepatic cells contained stainable fat but the large pale ones did not. There was no connective tissue proliferation although there was some cellular infiltration present in the areas of collapse immediately adjoining the central veins. In such areas there was a slight amount of condensation of reticulum. The reticulum framework was disintegrated in the areas occupied by the large pale cells.

The sections of the livers of the animals treated with carbon tetrachloride alone revealed changes in the hepatic cells similar to those observed at the end of the first week. However, the degree of central collapse was greater and there was a greater degree of cellular infiltration. These cells again consisted of lymphocytes, histiocytes and a few fibroblasts. Similar cellular elements extending in bands from the central areas toward the periphery of the lobules gave the sections the appearance of an early cirrhosis without cirrhosis actually being present (Fig. 4) as the Mallory-Heidenhain stained sections revealed only a few fibers of connective tissue. Instead the bands contained many entwined reticulum fibers. In the sections

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FIG. 1.—Liver of rat that received sulfanilamide and inhalations of carbon tetrachloride daily for 1 week. The cells about the central vein are enlarged and vacuolated. The nuclei are pyknotic (H and E, $\times 100$).

FIG. 2.—Liver of rat that received only inhalations of carbon tetrachloride daily for 1 week. The damage is more extensive and there is a greater degree of cellular infiltration than in the section in Figure 1, though the exposure to carbon tetrachloride was exactly similar in the 2 instances (H and E, $\times 100$).

FIG. 3.—Liver of rat that received sulfanilamide and inhalations of carbon tetrachloride daily for 2 weeks. The most severely damaged cells are the large pale ones with eccentrically placed pyknotic nuclei (H and E, $\times 100$).



stained with Sudan IV, many droplets of fat were present only in those enlarged cells which were vacuolated in the sections stained with hematoxylin-eosin.

Effect of Sulfanilamide Following Damage by Carbon Tetrachloride. Fifteen animals were exposed to fumes of carbon tetrachloride for 30 minutes daily for 1 week. Necropsy was performed on 3 of the animals at the end of this time and portions of the livers were removed for microscopic examination. Hepatic damage (Fig. 2) was present. The remaining 12 animals were divided into two equal groups. Sulfanilamide was given daily to one group until the animals were killed for necropsy, while the remaining group of 6 animals served as controls. Necropsy was performed on 3 animals from each group at the end of the first and the second week, respectively, following discontinuance of administration of carbon tetrachloride.

Grossly there was no difference in the appearance of the livers of these two groups, except for the darker color of the livers of the group which received sulfanilamide. Examination of microscopic sections did not reveal any evidence of central necrosis or deposition of fat in either group at either period, indicating that hepatic regeneration had occurred satisfactorily in both groups. Administration of sulfanilamide had not impeded regeneration (Fig. 5).

Effect of Alcohol and Sulfanilamide Administered Simultaneously. Eighteen animals received 6 cc. of a 20% solution of alcohol daily by means of stomach tube. Half of these animals (*i. e.*, 9) received sulfanilamide in addition to the alcohol. Necropsy was performed on 3 animals from each of the two groups at the end of the second, the third and the fourth week respectively, of the experiment.

Examination of sections of livers of both groups of animals did not reveal any evidence of damage of hepatic cells, of proliferation of connective tissue or of interruption of the reticular framework. Some of the hepatic cells at the periphery of the lobules in animals which received only alcohol contained droplets of fat (Fig. 6) but such deposition of fat did not occur in the livers of the group which received the sulfanilamide also.

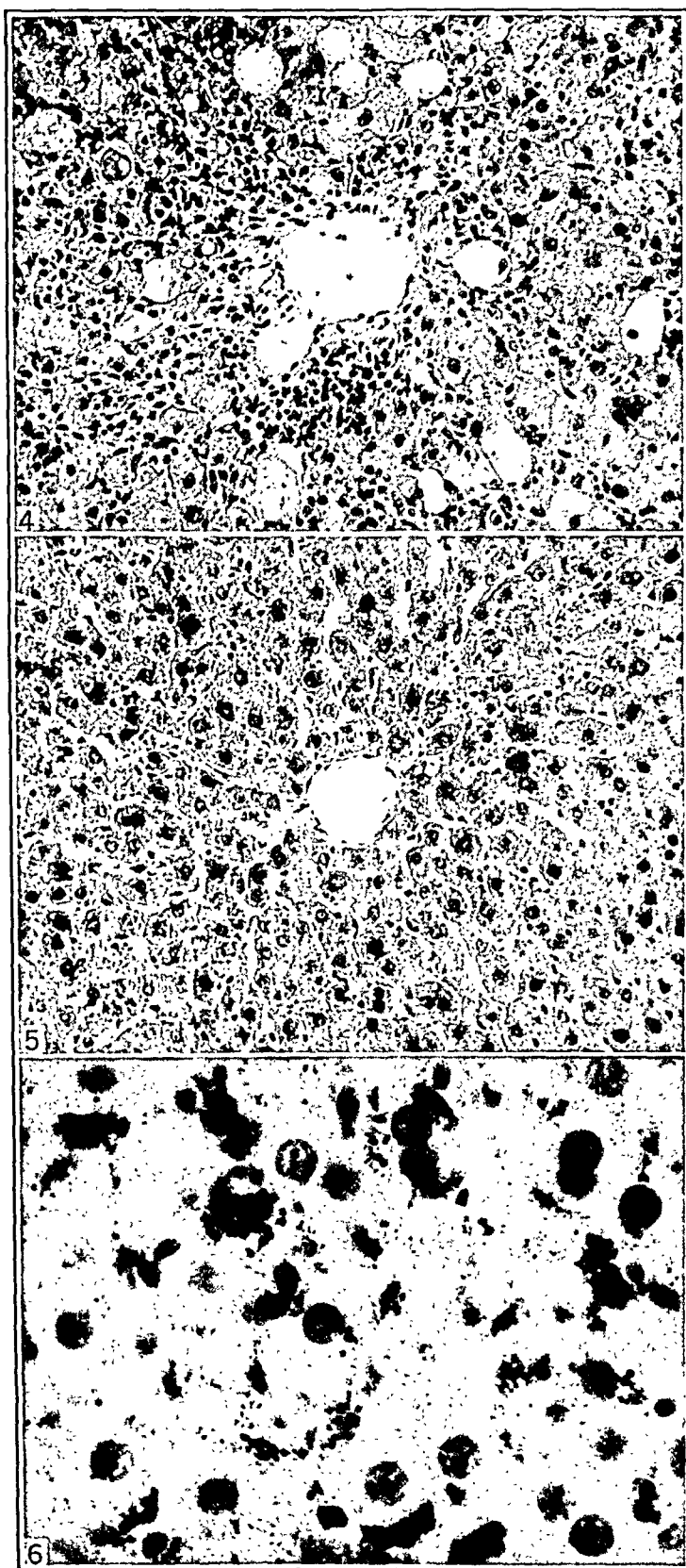
Effect of Sulfanilamide on the Liver in Obstructive Jaundice. To 9 of 18 animals in which the common ducts had been ligated, sulfanilamide was administered daily until the animals were killed for

LEGENDS FOR PLATE ON OPPOSITE PAGE.

FIG. 4.—Liver of rat that received only inhalations of carbon tetrachloride daily for 2 weeks. There is a greater degree of central collapse and cellular infiltration than in the section in Figure 3, though the exposure to carbon tetrachloride was exactly similar in the 2 instances (H and E, $\times 200$).

FIG. 5.—Liver of rat that received daily inhalations of carbon tetrachloride for 1 week and a daily administration of sulfanilamide for 2 weeks afterward. Complete restoration to normal was not impeded by the sulfanilamide (H and E, $\times 200$).

FIG. 6.—Liver of rat that received alcohol daily for 4 weeks. Note the deposition of globules of fat in the cells from the periphery of the lobule. Stainable fat was not present in the sections of the livers of animals that received sulfanilamide also (Fat Stain: Sudan IV, $\times 500$).



necropsy; the remaining 9 served as controls. The administration of the drug was begun on the day following operation. Necropsy was performed on 3 animals from each group at weekly intervals for 3 weeks and the livers were compared grossly and microscopically. Grossly, the livers of both groups were enlarged, firm and discolored with bile. In addition, the livers of the animals which had received sulfanilamide were black. The common and hepatic bile ducts were enormously distended in all cases. But microscopically no essential difference could be detected between these two groups of animals. There was no evidence of damage of the hepatic cells or of deposition of fat in any of the livers. Considerable proliferation of the bile ducts, most noticeable in animals living 3 weeks, was present to about the same degree in both groups.

Comment. The experiments cited here tend to indicate that the administration of sulfanilamide in moderately toxic doses does not increase the damage produced in the liver of a rat by carbon tetrachloride and that it does not impede regeneration of the liver after hepatitis has been induced by carbon tetrachloride. In fact, in the sections of the livers of the animals that had received both carbon tetrachloride and sulfanilamide, there was less damage than in those in which carbon tetrachloride had been administered alone. This observation is in accord with the recent report of Leach and Forbes that sulfonamide drugs act as protective agents against carbon tetrachloride poisoning. Furthermore, the simultaneous administration of alcohol with the sulfanilamide did not result in damage of the hepatic cells. Alcohol is regarded a substance which usually enhances the hepatotoxic effects of such drugs as phosphorus, chloroform or carbon tetrachloride. The drug likewise did not produce damage of the hepatic cells of animals that had obstructive jaundice. The livers of all animals that received sulfanilamide were dark brown or black as the result of contained blood discolored by the accumulation of various pigments responsible for cyanosis in animals or human beings receiving this drug.

These experimental data appear to be in accord with slowly accumulating clinical data which show that when sulfanilamide and allied compounds were administered to patients who had hepatic damage there were no apparent significant increases of hepatic dysfunction.^{3,4,5,6,8,16,19} However, they do not shed any light on the question why, when patients receive sulfanilamide, hepatitis develops in some cases but not in others. A depression of hepatic function among patients receiving sulfanilamide has been reported.^{15,21}

Conclusions. 1. The administration of sulfanilamide to a group of rats that were having hepatitis produced by inhalation of carbon tetrachloride did not increase the damage to the liver. On the contrary it appeared to lessen the damage.

2. Sulfanilamide after induction of hepatitis by means of carbon tetrachloride did not impede regeneration of the liver after administration of carbon tetrachloride had been discontinued.

3. The simultaneous administration of alcohol and sulfanilamide to rats did not result in damage of the hepatic cells, although in some of the animals that received only the alcohol fat was deposited in the liver.

4. The administration of sulfanilamide to animals that had obstructive jaundice did not produce any detectable injury to the livers not ascribable to biliary obstruction.

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CHANGES IN COPPER AND IRON RETENTION IN CHRONIC DISEASES ACCOMPANIED BY SECONDARY ANEMIA.

II. CHANGES IN LIVER, SPLEEN AND STOMACH.

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In a previous study,⁵ the retention of copper and iron in 146 patients with chronic diseases, predominantly malignancies, accom-

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panied by severe secondary anemia, was investigated. We found not only no shortage but actually a marked accumulation of these metals in the liver and spleen.

Gerlach³ showed that the amount of copper in benign tumors was normal but varied in malignant growths. Edlbacher and Gerlach¹ found that in Jensen sarcoma the copper content differed according to the part of the tumor studied, necrotic tumor tissue containing more copper than the growing tumor. Sümegi⁶ stated that in experimental rat cancer, copper was deposited in the liver and excluded from metabolism. He found 40% less copper than normal in the stomachs of his rats and interpreted this lack of copper as possibly responsible for inadequate formation of the anti-anemic factor.

Such a lack of copper in the stomach, if it were also present in human malignancies, might explain the accompanying anemia. We, therefore, studied stomach as well as liver and spleen tissue from malignant, non-malignant and normal cases.

Method. Copper was determined according to the method of McFarlane,⁴ with slight modifications, iron according to the modified method of Elvehjem and Hart.² All values are expressed as milligrams in 100 gm. of dry tissue. Since material in Montefiore Hospital is derived from chronic cases, normal values for copper and iron in liver, spleen and stomach were established from tissue obtained in case of accidental death from the Medical Examiner's office at Bellevue Hospital.

TABLE 1.—IRON AND COPPER CONTENT OF LIVER, SPLEEN, STOMACH AND TUMOR TISSUE IN SECONDARY ANEMIA.

Figures Represent Mg. in 100 Gm. of Dry Tissue (Averages in Parenthesis).

Type of disease with number of cases examined.	Liver.		Spleen.	
	Iron.	Copper.	Iron.	Copper.
Normal controls (15)	17 2-81 4 (44.7)	1.4-4 5 (2.8)	49 8-252 3 (137.2)	0.7-1.2 (0.9)
Malignancies (23)	12.5-1133 (124.2)	0.9-9 3 (3.8)	66 8-1776 (461.9)	0.8-3.6 (1.4)
Non-malignant cases (11)	29 0-247 0 (85.4)	1.5-7 2 (3.0)	61 9-721.8 (252.4)	0.8-2.7 (1.2)
Type of disease with number of cases examined.	Stomach.		Tumor tissue.	
	Iron.	Copper.	Iron.	Copper.
Normal controls (15)	16 3-20 7 (18.2)	1.1-1.4 (1.3)		
Malignancies (23)	6 0-79 9 (24.5)	1.1-2.2 (1.6)	17 7-130 1 (49.8)	1.2-4.2 (2.1)
Non-malignant cases (11)	19 3-137 8 (26.5)	0.8-2.3 (1.5)		

Findings. Iron in the spleen was greatly increased in about 50% of the malignancies, attaining levels in excess of 1000 mg. per 100 gm. of dry tissue, and up to 1776 mg. in a case of Hodgkin's disease. Copper storage in the spleen was either at the upper level of normal copper content, or exceeded it in 14 out of the 23 cases examined. Usually, greatly increased iron depots were paralleled by high copper

storage; there were instances, however, when iron was found to be normal in spite of a markedly increased copper content.

Iron in the liver was increased less frequently than in the spleen, only about one-third of the malignant cases showing high values. Copper storage was even less affected and exceeded the upper limit of normal in only 6 instances. But in these 6 a high copper level was not necessarily accompanied by a corresponding retention of iron. *Vice versa*, a level of 1133 mg. per 100 gm. of iron was associated with a normal copper value in a case of carcinoma of the ovaries.

Figures for iron in the stomach were at least normal in all and in excess of normal in 9 out of 16 cases. Usually, increased retention of iron was accompanied by increased retention of copper.

The striking affinity of tumor tissue for copper was demonstrated by values of 1.5 mg. per 100 gm. or more in 13 out of 18 tumors analyzed. Iron content ranged from 17.7 to 130.1 mg. per 100 gm., with the majority in the higher brackets. Material from a patient with Hodgkin's disease showed 1738 mg. of iron, but only 1.5 mg. of copper. This same case had 1776 mg. of iron in the spleen.

Iron and copper values in the non-malignant cases were in striking contrast to those encountered in malignancies. With few exceptions values for both elements were within normal in the spleen.

While levels of 479, 409.8 and 721.8 mg. per 100 gm. of iron were encountered in the spleen in instances of amyotrophic lateral sclerosis, arteriosclerosis and subacute bacterial endocarditis, respectively, they were exceptional. Similarly values of 1.4 and 2.7 mg. per 100 gm. of copper in the spleen in cases of coronary occlusion and essential hypertension respectively were also unusual. The liver showed a normal iron content in half and a normal copper content in all cases except in 1 of subacute bacterial endocarditis where 7.2 mg. were stored.

Iron in the stomach was elevated in all but 2 cases, though the only really high value was found in 1 of subacute bacterial endocarditis (137.8 mg.). Copper values were higher than normal in 6, normal in 4 and less than normal in 1 instance.

Discussion. It has been established that in severe secondary anemia there is not only no shortage, but actually a large accumulation of iron and copper in the liver and spleen. Extreme storage of these metals was found, especially in malignancies and marked retention in some non-malignant cases. Evidently a shortage of copper or iron or both could not be the prime factor responsible for anemia. Since a striking retention of iron and copper occurs in malignancies even without an accompanying anemia, anemia alone could not be responsible for the marked accumulation of these metals. Tumors and metastatic lesions showed marked accumulations of copper but these were not sufficiently large to explain the anemia.

Sümeği⁶ found 40% less copper than normal in the stomachs of rats with experimental cancer. The question arose whether there was interference with formation of the anti-anemic factor due to an inadequate amount of iron or copper in the stomach. We found sufficient or excessive amounts of these metals in the stomach, in the majority of the malignancies. Similarly, in the non-malignant cases with severe anemia there was no shortage of iron or copper in the stomach and there was moderate retention. While Sümeği's work may offer an explanation for the anemia of rat cancer, it does not hold for anemia in humans whose stomachs show normal copper and iron values in anemia.

No correlation could be found between the impairment of nutrition and the degree of retention of copper and iron. Nor was there any rule which metal would be stored, or if both were retained, which would be retained more, though retention of iron was more common than that of copper.

It appeared that in spite of adequate amounts of iron and copper in the stomach, liver and spleen, the power to synthesize the blood-forming elements was impaired. Under such conditions, large amounts of iron and copper stored for emergency purposes cannot be utilized in the conversion of inorganic iron into hemoglobin. This view explains the apparent paradox of severe anemia despite excessive copper and iron storage in the depot organs.

The most interesting feature of this and the previous work was the finding of storage of iron and copper out of all proportion to the anemia in malignancies, which reached its highest degree in extensive metastatic disease. The few cases of malignancies without anemia with enormous amounts of copper and iron in the liver and spleen show that such accumulation can occur even in the absence of anemia, with malignancy as the only apparent causative factor. The factors responsible for the extremely high storage of iron and copper in the liver and spleen in malignancies could not be determined. Nevertheless, this finding was so striking and constant as to be significant.

Summary. 1. The content of iron and copper in liver, spleen, stomach and tumor tissue in chronic diseases accompanied by secondary anemia has been studied.

2. There is not only no shortage, but actually a large accumulation of iron and copper in liver and spleen in many cases of anemia. Extreme storage was found especially in malignancies, but was dependent on some factor other than the anemia.

3. Insufficient formation of the anti-anemic factor due to inadequate storage of iron or copper in the stomach suggested by Sümeği could not be the factor responsible for the anemia since at least normal, and in most cases higher than normal, amounts of these elements were present in the stomach.

4. Tumor tissue showed a high percentage of copper, indicating a

marked affinity for this element. This could not, however, have played a rôle in the production of anemia.

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PORTAL CIRRHOSIS.

A CORRELATION OF CLINICAL, LABORATORY, PERITONEOSCOPIC
AND AUTOPSY FINDINGS.

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DURING the past year, the opportunity has been presented for the study of 24 cases of hepatic disease that have proven to be portal cirrhosis of the liver in varying stages of development. Clinical and laboratory data together with peritoneoscopy and postmortem examinations were used in determining the diagnosis. An attempt to correlate the clinical and laboratory data has led to some observations which we consider of significance.

In the series of 24 cases, peritoneoscopic examination was performed in 20 cases, with postmortem examination being done on 3 of these cases. In 4 cases, postmortem examination alone was performed.

In order to simplify our results, we have adopted the classification of cirrhosis of the liver formulated by Connor³ in a recent article. This classification appears to be in accord with most of the recent clinical and pathologic developments in the field of liver disease. He divides portal cirrhosis or chronic diffuse fibrosis of the liver into three main types.

1. Biliary cirrhosis, which is usually associated with biliary obstruction. The lesions begin in the portal areas around the bile ducts and the liver is usually large, tense, green and may be nodular.

2. Pigment cirrhosis, which is usually associated with the collection of irritating pigments and metals-around the periphery of the

liver lobule. This is associated with periportal connective tissue proliferation. The liver is not usually decreased in size and has a smooth surface.

3. Fatty cirrhosis, in which the lesions develop around the lobule resulting from the fatty degeneration of cells around the periphery of the lobule, followed by fibroblastic proliferation. This type can be divided into three phases: (a) Acute fatty liver which occurs in the 40 to 45 age group. The liver is large, pale and greasy containing 60% fat and is usually smooth. This stage is also called fatty metamorphosis of the liver. (b) Fatty liver with early perilobular fibrosis which occurs in the 45 to 55 age group. The liver is large or normal and may be lobulated or smooth. This corresponds to hypertrophic fatty cirrhosis. (c) The atrophic phase or classical Laennec's cirrhosis in which the liver is smaller and grossly nodular and usually has a thickened capsule. This occurs in the 55 to 65 age group.

All of the 24 cases fall into the classification of portal cirrhosis. One case was the pigmentary type of cirrhosis, associated with sickle-cell anemia. Two of the cases fell into the classification of acute fatty liver or fatty metamorphosis. There were 16 cases of hypertrophic fatty cirrhosis and 5 cases of atrophic portal cirrhosis.

The diagnostic observations of the liver were performed by the peritoneoscopy service of Dr. LeRoy Sloan and Dr. Frank De Trana at the Cook County Hospital. The procedure of peritoneoscopy has been repopularized recently by Ruddock.¹¹ By this method direct endoscopic visualization of the liver is possible and in the hands of the trained observer, a definite diagnosis of the types of liver disease can usually be made, especially if it is the portal type of cirrhosis. This procedure is open to the criticism that biopsies are not made, although this can be done with the proper equipment, and that a histologic diagnosis is not obtained. However, peritoneoscopy is a relatively safe and convenient method for examining the peritoneal cavity and some of its contents, especially the liver. In cases of ascites or hepatomegaly of undetermined origin, it is often of great diagnostic aid.

A summary of the cases revealed that there were 19 men (16 white and 3 negro) and 5 women (3 white and 2 colored). The ages ranged from 17 to 75 years with 15 (62.5%) present in the fourth and fifth decades of life. Eighteen of the cases (75%) had a definite history of chronic alcoholism. Four cases had a history of syphilis, and of these, 2 had had indifferent treatment.

A review of the physical findings showed that all 24 cases had a usually well marked hepatomegaly and the liver extended 2 to 6 finger-breadths below the right costal margin. If the liver could not be palpated due to severe ascites, it could always be felt after paracentesis. The spleen was palpable in 6 of 24 cases (25%). Jaundice could be divided into three phases. Seven cases (29%)

had severe jaundice; 7 (29%) had moderate jaundice and 5 (20%) were subicteric. Upon correlating the type of liver disease with jaundice, it was found that in the one case of pigment cirrhosis associated with sickle-cell anemia, jaundice was the most prominent feature in the history, having been noted for 6 years before admission. In the 2 cases of acute fatty liver, or fatty metamorphosis, jaundice was marked on examination and prominent in the case history. In the 16 cases of hypertrophic fatty cirrhosis, jaundice was marked in both the history and physical examination in 7 of the cases, and was not prominent in the others. There were 5 cases of atrophic portal cirrhosis, in 3 of which jaundice was prominent in both the history and physical findings. Only 14 cases, (60%) exhibited marked ascites, and here the physical findings were misleading in that abdominal enlargement and other signs of fluid did not always indicate ascites when paracentesis was performed with the peritoneoscope. Pectoral alopecia was present in 6 of the 19 males (31%).

Thus the characteristic picture of the patient with portal cirrhosis was that of a male in the fourth and fifth decade of life, usually having a history of chronic alcoholism, always presenting a palpable liver and usually jaundice and ascites.

A summary of the laboratory data revealed some interesting findings. Examination of the blood revealed that 23 cases (96%) had some degree of anemia. In 16 cases (67%) an anemia characterized by macrocytosis or hyperchromia or both, was present. Six cases (25%) had some degree of secondary anemia, usually microcytic and hypochromic in nature. One case had a typical severe sickle-cell anemia and in one case no anemia was demonstrable.

The frequency of serum protein changes in parenchymal liver disease is well known, and this fact is borne out in our series of cases. The serum albumin fraction was less than normal in 23 of 24 cases (96%). The total serum protein was less than normal in only 3 of 24 cases (12½%). The serum globulin fraction was elevated in 21 of 24 cases (87%). If the normal albumin globulin ratio is considered to be 2:1, then the ratio was lowered in all 24 cases and totally reversed (*i. e.*, less than 1) in 16 of 24 cases (67%). Thus it can be seen that in this series of cases, the serum protein changes were profound.

The icteric indices of all 24 cases were above the normal level of 4 to 6, and varied from 9 to 150. Icteric indices above 10 were found in 21 of 24 cases. These findings appear to point out the frequency with which jaundice is associated with portal cirrhosis.

The hippuric acid test showed deficient liver function in 18 of 21 cases in which 2 was determined, (86%). There appeared to be a moderate correlation between the hippuric acid test and serum protein determinations as to the severity of liver damage. A bromsulphalein test was performed in one case and a glucose tolerance test in another, both showing evidence of decreased liver function.

TABLE 1.—SUMMARY OF DATA ON 24 CASES OF CIRRHOSIS.

Patient No. Color	Hx and physical examination	Blood findings*	Total* serum protein.	Serum albumin.	Serum globulin.	Albumin globulin ratio.	Icteric index.	Liver function tests.	Pathologic diagnosis of liver (by peritoneoscopy unless otherwise stated).
1. F. G. 52 W M	Alcoholism 1+ Symptoms 2 yrs. incl. jaundice PX.—Jaundice 2 Pect. alopecia 0 Liver 5F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 56% RBC 2,810,000 WBC 10,400 Anisocytosis Macrocytosis Hypochromia	6.34	2.34	4.01	58	51 44	Hippuric acid† 0.72 gm.	Enlarged, light gray, hobnailed. Hypert. portal cirrhosis.
2. F. C. 42 C M	Luces. Moderate Rx Alcoholism 1+ Symptoms 2 mos. PX.—Subicteric Pect. alopecia 4+ Ascites 4+ Liver 5F down Spleen + Abd. veins 3+	Hgb 39% RBC 2,800,000 WBC 7200 Hypochromia Microcytosis Polychromatophilia	8.98	3.27	5.71	57	17	Hippuric acid 3.34 gm.	Typical, hobnailed. Hy- Marked ascites. Hy- pert. portal cirrhosis. Confirmed by autopsy 6 mos. later.
3. T. N. 54 W M	Alcoholism 0 Symptoms 2 mos. PX.—Subicteric Pect. alopecia 0 Ascites 4+ Liver 1F down Spleen 0 Abd. veins 2+	Hgb. 63% RBC 3,290,000 WBC 4000 Anisocytosis Macrocytosis	6.44	3.22	3.22	1.00	10	Hippuric acid 0.75 gm.	Enlarged, hobnailed. Marked ascites. Hy- pert. portal cirrhosis.
1. C. Z. 50 W M	Alcoholism 4+ Symptoms 1 mo. incl. icterus PX.—Jaundice 2+ Pect. alopecia 4+ Liver 6F down Ascites 3+ Spleen 0 Abd. veins 2+	Hgb 45% RBC 2,770,000 WBC 3650 Anisocytosis Macrocytosis	7.31	3.31	4.01	80	50 51	Hippuric acid 2.37 gm.	Enlarged, dark yellow- ish-brown. Capsule is studded with translu- cent, pinhead-sized nod- ules. Fatty metamor- phosis of liver. Tuber- culous peritonitis.

No.	Sex	Age	Chief Complaints	Hb	RBC	WBC	Diff.	Spleen	Liver	Kidney	Bladder	Uterus	Vagina	Rectum	Stool	Urine	Other
39	W	39	Symptoms 2 yrs. PX.—Jaundice 1+ Pect. alopecia 4+ Liver 3F down Ascites 2+ Spleen 0 Abd. veins 4+	55	2,110,000	4900	Normal	0	3F down	0	0	0	0	0	0	0	0
52	W	52	Alcoholism 3+ Symptoms 2 mos. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 4+ Caput medusa Spleen 0	55	2,590,000	11,200	Macrocytosis	0	3F down	0	0	0	0	0	0	0	0
28	C	28	Alcoholism 0 Nine pregnancies Symptoms 4 mos. incl. jaundice PX.—Jaundice 2-3+ Liver 3F down Ascites 0 Spleen + Abd. veins 0	45	3,040,000	7400	Diff. normal	0	3F down	0	0	0	0	0	0	0	0
45	W	45	Alcoholism 4+ Symptoms 1 mo. PX.—Jaundice 0 Pect. alopecia 0 Liver 5F down Ascites 0 Spleen 0 Abd. veins 1+ Old appendect. scar	59	2,840,000	4400	Diff. normal	0	5F down	0	0	0	0	0	0	0	0

TABLE 1.—(Continued)

Parent Age Sex Color	History and Physical examination.	Blood findings.	Total serum protein.	Serum albumin.	Serum globulin.	Albumin globulin ratio.	Icteric index.	Liver function tests.	Pathologic diagnosis of liver (by peritoneoscopy, unless otherwise stated).
C. C. 52 W M	Alcoholism 1+ Symptoms 6 wks. incl. jaundice 1+ PX.—jaundice + Pect. alopecia + Liver 5F down Ascites 1+ Spleen 0 Abd. veins 3+	Hgb 23% RBC 2,750,000 WBC 14,200 Anisocytosis Macrocytosis	7.65	2.65	5.00	53	100 150	Hippuric acid 0 gm.	Enlarged, surface finely granular. Marked as- cites. Hypert. portal cirrhosis.
			5.60	2.81	2.85	85	.99	Hippuric acid 1.41 gm. Wass. and Kahn negative	Enlarged, dark gray green and hobnailed. Also simple cyst, rt. lobe. Hypert. portal cirrhosis.
10. D. O. 48 W M	Alcoholism 1+ Lues with no Rx Symptoms 2 yrs. incl. jaundice 3+ PX.—jaundice Pect. alopecia Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 73% RBC 3,500,000 WBC 8200 Diff. normal						Hippuric acid 2.21 gm. Kahn neg.	Enlarged and hobnailed. Gall bladder distended. and wall thickened. Hypert. portal cirrho- sis. Chr. cholecystitis.
11. W. W. 48 W M	Alcoholism 4+ Lues with moderate Rx Symptoms 1 yr. incl. jaundice 3+ PX.—jaundice + Pect. alopecia + Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 69% RBC 3,500,000 WBC 8200 Diff. normal	8.34	3.12	5.22	59	60	Hippuric acid 1.56 gm.	Coursely hobnailed. Gall bladder normal. Marked ascites. Explora- tory laparotomy, Tal- maoper. portal cirrhosis. Autopsy 1 mo. later, atrop. portal cirrhosis.
12. D. P. 52 C F	Alcoholism 4+ Symptoms 1 mo. incl. jaundice 3+ PX.—jaundice 3+ Liver 3F down	Hgb 84% RBC 5,100,000 WBC 5900 Diff. normal	7.81	3.75	4.06	.92	75	Hippuric acid 1.56 gm.	

13. J. C. 52 W M	Alcoholism 1+ Symptoms 1 mo. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 97% RBC 4,580,000 WBC 10,000 Anisocytosis Macrocytosis Hyperchromia	8.99	5.31	3.68	1.71	18.5	Hippuric acid 2.89 gm. Glucose toler. test, normal curve	Enlarged, finely granular. No fluid present. Early hypert. portal cirrhosis.
14. C. Y. 56 W M	Alcoholism 2+ Symptoms 2 wks. PX.—Subicteric Pect. alopecia 0 Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 60% RBC 2,660,000 WBC 13,200 Anisocytosis Macrocytosis Hyperchromia	5.85	3.75	2.10	1.78	18.7	Glucose toler. test shows hyperglycemic curve Bl. cholest. 208 Bl. cholest. esters 59	Enlarged, finely granular. No ascites. Hypert. portal cirrhosis.
15. W. G. 72 C M	Alcoholism 3+ Luces denied Symptoms 1 mo. PX.—Subicteric Pect. alopecia Liver 2F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 75% RBC 3,800,000 WBC 5450 Anisocytosis Macrocytosis	8.65	2.34	5.31	.44	18.7	Hippuric acid 1.53 gm. Kahn 2+ Wass. 4+	Smaller than normal; diffuse hobnail. Marked ascites. Atrophic portal cirrhosis.
16. J. D. 62 W M	Alcoholism 3+ Symptoms 1 mo. incl. jaundice PX.—Jaundice 2+ Pect. alopecia 0 Liver 4F down Ascites 2+ Spleen 0 Abd. veins 1+	Hgb 80% RBC 4,130,000 WBC 12,500 Anisocytosis Macrocytosis	7.81	3.85	3.96	.97	50	Hippuric acid 1.06 gm.	Enlarged, has typical granular appearance. Sl. ascites. Hypert. portal cirrhosis.
17. I. S. 50 W F	Alcoholism 2+ Symptoms 1 mo. incl. jaundice PX.—Jaundice 2+ Liver 4F down Ascites 2+ Spleen 0 Abd. veins 3+	Hgb 44% RBC 1,910,000 WBC 8250 Macrocytosis	7.99	2.56	5.43	.49	30	Hippuric acid 1.01 gm.	Enlarged and finely hobnailed. Hypert. portal cirrhosis.

TABLE 1.—(continued)

22. G. N. 75 W M	Alcoholism 4+ Symptoms 2 yrs. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 4+ Spleen 0 Abd. veins 0	Hgb 51% RBC 3,690,000 WBC 10,750 Hyperchromia Anisocytosis Poikilocytosis	6.64	3.60	3.04	1.18	9	Bromsulphalein test, 75% reten- tion	Autopsy: atrophic peri- portal cirrhosis and adenocarc. of cecum with metastases to the liver.
23. E. W. 17 C M	Alcoholism 0 Jaundice for sev. yrs., abd. enlargement PX.—Jaundice 4+ Pect. alopecia Liver 6F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 27% RBC 1,500,000 WBC 25,000 Anisocytosis Poikilocytosis 75% sickling of red blood cells	7.50	3.48	4.02	.85	150	Bl. cholest. 101 Wass. negative	Autopsy: Marked jaun- dice and periportal (hy- pertrophic) type of cir- rhosis of pigmentary etiology.
24. D. W. 64 W M	Alcoholism 0 Symptoms 3 mos. incl. jaundice PX.—Jaundice 2+ Pect. alopecia 0 Liver 2F down Ascites 1+ Spleen 2+ Abd. veins 1+	Hgb 43% RBC 2,105,000 WBC 3700 Hyperchromia Anisocytosis Poikilocytosis	7.19	3.80	3.39	1.12	37.5	Hippuric acid 2.71 gm.	Autopsy: Atrophic fatty portal cirrhosis of liver. Jaundice.

* The serum proteins were determined by the modified method of Kraus (J. Lab. and Clin. Med., 25, 1300, 1940).

† The hippuric acid determinations were estimated by a modified method of Kraus and Dulkan (J. Lab. and Clin. Med., 26, 729, 1941). Normal excretion of hippuric acid in 4 hours when 5.9 gm. of sodium benzoate are fed is estimated as from 3 to 5 gm. Unless otherwise indicated, the blood serological tests were negative.

Thus, 20 of 23 cases (83%) showed decrease in liver function as determined by the hippuric acid, bromsulphalein and glucose tolerance test, whereas the serum protein tests showed liver damage in all cases.

Discussion. The correlation of data collected in this study has brought up some points that we wish to stress.

First, the correlation between alcoholism and cirrhosis in man is noted in our cases, as it has been elsewhere. However, it is well to remember that, as yet, no one has produced portal cirrhosis experimentally by the use of alcohol. In a recent article, Mallory⁹ discussed various toxic substances which are known to cause parenchymal liver disease such as halogenated hydrocarbons, arsphenamine, selenium, and so on, and states that alcohol cannot yet be called the cause of portal cirrhosis.

The association of jaundice with portal cirrhosis, we feel, has not received sufficient consideration. It has been our impression that students have been taught that jaundice is not frequently associated with portal cirrhosis of the liver, and that when it does occur, it is a late or terminal manifestation. Richard Cabot classifies jaundice in his book "Differential Diagnosis." Excluding icterus neonatorum and sepsis of 661 cases of jaundice, only in 48 (7.1%) was the cause considered to be portal cirrhosis, which would tend to substantiate the above belief. In Tice's "Practice of Medicine," the section on diseases of the liver by Elliot and Nadler states that jaundice is not a prominent feature of portal cirrhosis, but that it is encountered at some stage in over one-third of the cases. Samuel Weiss in his book, "Diseases of the Liver, Gall Bladder, Ducts and Pancreas," states that early in the course of portal cirrhosis jaundice is not usually present. Later, when hepatic insufficiency is pronounced, there is said to be a subicteric tint to the skin, or the patient may be jaundiced, and also if jaundice occurs at all, it is of the catarrhal type and considered a complication.

Foley, Keeton, Kendrick and Darling¹⁰ reported 21 cases of liver disease and an analysis of their cases revealed that 20 out of 21 had higher icteric indices than normal. All of the cases were portal cirrhosis, except one of acute yellow atrophy. However, this finding was not stressed in their paper.

We have noted the frequency of jaundice in our series of cases. It did not appear to be related to the duration of the disease, and in fact occurred in the early stages of portal cirrhosis (*i. e.*, the acute fatty liver and the hypertrophic fatty stage) as frequently as in the later stages. The history of the onset of jaundice is often difficult to obtain, but it is frequently one of the earliest and most prominent symptoms in the case history. This high incidence of jaundice would lead us to the impression that liver damage of sufficient nature to cause a regurgitant or toxic type of jaundice may occur relatively early in the course of portal cirrhosis. This can be noted in the

correlation of the presence of jaundice with the various phases of portal cirrhosis. From the viewpoint of pathogenesis, it is believed that actual damage to the liver cells is the first step in the development of portal cirrhosis. Fibrosis and regeneration of the liver cells occurs later and it is reasonable to assume that decrease of liver function and jaundice, which is an expression of this, can occur early in portal cirrhosis, and may be progressive or intermittent, depending on the regenerative ability of the liver. The progression of the earlier forms of liver damage, such as the so-called catarrhal jaundice, simple jaundice, and so on. to the chronic stages of liver disease, has been observed clinically by Bloomfield² and other observers. He has been able to demonstrate that portal cirrhosis may begin as a catarrhal jaundice, and that acute exacerbations of "hepatitis," characterized by jaundice, can occur during the course of the disease. This fits in with the experimental observations on cirrhosis and tends to confirm our impression of the presence of jaundice during the course of this disease.

We have noted that 96% of this series of cases exhibited some degree of anemia, 67% of which was macrocytic or hyperchromic in type. However, this association of marked anemia with cirrhosis and other chronic liver disease has not been greatly emphasized until very recently. Wintrobe,¹⁴ however, found that in 44 cases of cirrhosis, 41% had a macrocytic anemia, 34% had a normocytic anemia and 9% had a hypochromic anemia. This anemia was attributed to the failure of storage of extrinsic factor in the liver, due to the pathologic changes present. Bianco and Jolliffe,¹ in a study of the anemia of the alcohol addict, observed that in 30 patients with alcoholic cirrhosis, 70% were anemic, and in 53% this anemia was macrocytic in type and associated with hyperchromia. They attributed the anemia to extrinsic deficiency of some necessary hematopoietic substance required to maintain normocytosis.

The alteration of serum proteins in diseases of the liver, particularly portal cirrhosis, has been well-known since the work of Grenet⁷ and Gilbert and Cheray.⁶ Numerous investigators have reported the lowering of total serum protein, especially of the albumin fraction, and the lowering or reversal of the albumin globulin ratio. Meyers and Keefer¹⁰ and Foley, *et al.*,^{5a} have reported such changes as occurring in all of their cases of portal cirrhosis, and also other types of chronic liver disease. Tumen and Bockus¹³ reported 45 cases of acute and chronic liver disease in which hypoalbuminemia was the most constant feature noted, being present at some time in practically every case of chronic advanced liver disease and in most cases of obstructive jaundice. They found an elevation of the serum globulin and a lowering of the albumin globulin ratio usually present but did not think this as significant as a lowering of the serum albumin.

Our results coincide with previous findings as regards the lowering

of serum protein, especially the albumin fraction and a rise of the globulin fraction, with reversal of the albumin globulin ratio. The serum protein determinations appear to be the most constant and perhaps earliest means of determining the severity of liver damage, as borne out by the results in comparison with other liver function tests.

In this connection it is interesting to note the work of Kirshbaum and Popper,⁸ in a series of cases of toxic hepatitis of a form intermediate between so-called catarrhal jaundice and acute yellow atrophy. They found changes consisting of enlargement of the liver and characterized histologically by damage to the liver cells and a serous hepatitis with dissociation of the liver cord cells. Edema of the liver was marked due to the fact that the Disse spaces, between the blood capillaries and the liver cord cells, were markedly widened and contained coagulated proteins. The presence of these proteins led to the assumption that there was capillary damage with exudation of serum protein, and the damage was assumed to be due to the toxic agent present. When the amount of escaped protein was high, there was an increasing accumulation of fluid between the cords of liver cells, due to the decrease of the colloid osmotic pressure of the blood. This fluid pressure finally destroyed the structure of the liver cells, giving the picture of severe dissociation. This was synonymous with "serous hepatitis" which occurs in the severest form in the liver of beriberi. This may be a possible explanation for the serum protein changes in parenchymatous liver disease, for here is an actual loss of blood protein from the circulation. Since the liver is tied up with the intermediary metabolism of serum protein, especially albumin, the actual liver damage would prevent or inhibit the reformation of the lost protein.

In a series of dogs, Elman and Heifetz⁴ produced a 50% fall in the albumin fraction of the plasma by dietary means, without a change in the globulin. As the hypoalbuminemia progressed there were severe changes in the liver, consisting of increase of the water content and a fall in the protein content and vacuolation of the liver cells. There was definite impairment of liver function. Thus we have corollary evidence of the effect of protein deficiency on the liver and on the serum protein levels.

It would seem plausible then to state that there are two factors concerned in the pathogenesis of portal cirrhosis. One is the dietary deficiency of protein, which appears to be prominent in the cirrhotic as evidenced by fall in serum protein, especially of albumin and the change in the albumin globulin ratio. The presence of macrocytic anemia, neurologic manifestations and often frank pellagra in the cirrhotic also points to this, as has been emphasized by Snell.¹² The prominence of alcoholism in the case history is explained by the fact that many alcoholics subsist on very little food during their debauches. Also, cirrhosis of the liver is endemic in regions where widespread nutritional deficiencies are common, as in

China. The work of Elman and Heifetz is corollary evidence that nutritional deficiency of protein alone can cause liver damage.

We have reviewed pathologic evidence that certain toxins can affect the liver by causing capillary damage and exudation of serum protein. It would seem logical to assume that a combination of the two factors of protein deficiency and toxic capillary damage in the liver could explain the pathologic picture of early liver damage and that a progression of these changes would eventually lead to a classical portal cirrhosis.

Summary. A series of 24 cases of portal cirrhosis of the liver in varying stages was studied in an attempt to correlate clinical and laboratory findings. The diagnosis was confirmed by peritoneoscopy in 20 cases and by postmortem examination in 4 cases. Marked change in the serum albumin and globulin were noted in 100% of the cases. There was a marked tendency to the lowering of the serum albumin and a rise of the serum globulin with a consequent lowering of the albumin globulin ratio in all cases. There was a reversal of the albumin globulin ratio in two-thirds of the cases. Jaundice was a fairly constant feature being present in some degree, as measured by the icteric index in all cases. Jaundice was evident on physical examination in 79% of the cases. Changes in the peripheral blood were marked in 96% of the cases. A macrocytic or hyperchromic anemia was present in 67% of the cases while 25% exhibited a microcytic or hypochromic anemia. One case presented a typical severe sickle-cell anemia. Deficiency of liver function, as determined mainly by the hippuric acid test and also by a glucose tolerance and a bromsulphalein test, was noted in 83% of the cases. When the serum protein determinations were utilized as a liver function test, 100% of the cases exhibited a diminution of liver function.

A correlation of clinical and laboratory findings together with peritoneoscopic examination of the liver and postmortem analysis would appear to offer useful fields of investigation in liver disease.

A possible explanation of some etiologic factors in portal cirrhosis damage to liver cells, toxic hepatitis, catarrhal jaundice, acute yellow atrophy is offered.

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TREATMENT, COMPLICATIONS AND DEATHS IN 753 CASES OF CLINICAL DIPHTHERIA.

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BETWEEN July 1, 1937, and June 30, 1940, there were 753 cases of diphtheria admitted to the Los Angeles County General Hospital, of whom 48% were males and 52% were females. The admissions have followed a consistent downward trend each year since 1932, though the comparative yearly mortality for the period studied showed no appreciable difference (5% for the first 2 years as compared to 4.2% for the last year). This decline in incidence may well be due to natural trends as well as to an extensive immunization program.

Age Distribution with Deaths and Fatality Rate. Table 1 shows the age distribution of cases, the number of deaths in each group, and the fatality rate. Note that the incidence of diphtheria under one year of age was extremely low. The majority of cases (61%) occurred before the age of 10, the subsequent incidence gradually diminishing to the age of 65. This is similar to the published reports of Gordon⁶ in Detroit and of Hoyne⁷ in Chicago. The case fatality rate showed no marked difference for the small number of cases. The infant fatality rate was 41.6%. There were only 2 deaths after the age of 15; one was a male age 37, a chronic alcoholic ill for 7 days before admission, and the other a male age 47 ill 8 days before admission and who died within 4 hours after admission.

Duration of Illness Before Administration of Antitoxin. Of our patients 60% were admitted on or before the third day of their illness and the average time before the administration of antitoxin in 713 cases was 3.7 days. In 40 cases the duration was unknown. Among the fatal cases the average time was 5 days, which bears out the frequently observed fact of increasing risk after the third day of illness.

TABLE 1.—DISTRIBUTION OF CASES AND DEATHS ACCORDING TO AGE GROUPS.

Age.	Cases.	Deaths.	Case fatality rate %.
0-1	12	5	41.6
1-5	229	18	7.8
5-10	218	9	4.1
10-15	80	2	2.5
15-20	52	0	0
20-25	43	0	0
25-30	50	0	0
30-35	19	0	0
35-40	22	1	4.5
40-45	10	0	0
45-50	9	1	11.1
50-55	4	0	0
55-60	2	0	0
60-65	3	0	0
Total	753	36	4.8

Distribution of Lesions. Of our cases 53% were simple tonsillar diphtheria. There were no deaths in this group and none in the few cases of nasal pharyngeal or pharyngeal diphtheria. One case of diphtheria limited to the eye and one case in a burn associated with scarlet fever were noted: the former required enucleation and the latter skin grafts; both recovered. Table 2 shows the distribution of cases with location of the membrane, the presence of the "bull neck" type of infection, and the mortality in the separate groups. The fatality rate is high in the group so aptly described as "bull neck." In these patients the tissues of the neck externally and internally show marked edema and induration as well as lymphadenopathy. The membrane tends to spread rapidly and assume a dirty, necrotic appearance, and often the involvement is so extensive that the airway is obstructed through the nostrils and pharynx. In such cases increased pulse rate associated with increased respiration and temperature are regarded as indications for tracheotomy even without suprasternal retractions or cyanosis. Experience teaches that intubation is unwise in these cases. There was a mortality of 100% in 9 cases of the "bull neck" type in which the membrane extended into the larynx, trachea, and bronchi.

Dosage of Antitoxin. The dosage of antitoxin was determined by the apparent toxemia, the extent of the membrane, and the duration of the illness; neither weight nor age was used as a criterion. Twenty-eight per cent each of the total of 753 patients received 20,000, 30,000, and 40,000 units respectively; less than 4% received less than 20,000 units, and 12% received varying amounts over 40,000 units. Laryngeal cases were never given less than 40,000 units. Two patients did not receive antitoxin; one of these was moribund and died within an hour, and the other had almost recovered when admitted to the hospital.

General Therapy. Therapy in the early stages of diphtheria consists in adequate doses of antitoxin, complete bed rest, constant

nursing care, an adequate dietary and vitamin regimen, and intravenous dextrose and insulin. The diagnosis is determined as rapidly as possible and treatment is begun in the admitting ward. If the skin test for serum sensitivity is negative, intramuscular antitoxin is given $\frac{1}{2}$ hour later; severely toxic patients may receive intravenous antitoxin diluted in 200 cc. to 400 cc. of physiologic saline. Dextrose

TABLE 2.—DISTRIBUTION OF MEMBRANE AMONG CASES WITH MORTALITY OF EACH VARIETY.

Type.	Bull neck.		Case fatality, rate %.	Total.		Case fatality, rate %.
	Cases.	Deaths.		Cases.	Deaths.	
Nasal	0	0	0 0	48	1	2.1
Nasal	0	0	0 0	13	0	0 0
Pharyngeal						
Nasal	9	5	55.5	48	6	12.5
Tonsillar						
Pharyngeal	11	0	0.0	401	0	0.0
Tonsillar	25	7	28.0	111	7	6.3
Pharyngeal						
Pharyngeal	0	0	0.0	8	0	0.0
Tonsillar	1	1	100.0	59	6	10.2
Pharyngeal						
Laryngeal	3	3	100.0	19	4	21.1
Nasal						
Tonsillar	5	5	100.0	8	8	100.0
Pharyngeal						
Laryngeal	0	0	0.0	36	4	11.1
Tracheo						
Bronchial	0	0	0.0	1	0	0.0
Laryngeal						
Comp. wound	0	0	0.0	1	0	0.0
Scarlet	0	0	0.0	1	0	0.0
Eye						
Total	54	21	38.8	753	36	4.8

solution is never used; it precipitates the antitoxin. All patients are placed at absolute flat bed rest, and, where necessary, in Trendelenburg position for postural drainage. Patients placed with their heads down must be watched with extreme care, as plugs may form in the bronchi. In some instances such plugs have required bronchoscopic removal to save life. Ordinarily, after a short period of drainage it is better to keep the patient flat, and in some instances it has proved beneficial to instill a drop or two of normal sterile saline through the tube at short intervals in tracheotomized cases. Since instituting this method, we have had remarkable freedom from the drying out effect and complicating mucous plugs resulting therefrom. Fluids are forced, especially in the form of dextrose; if necessary, this is given intravenously. Vitamin B complex and vitamin C are given in large doses. Barbiturates and bromides are used to alleviate restlessness; opiates are avoided.

Complications. *Myocarditis.* Circulatory failure associated with toxic myocarditis is an important problem because of the large number of deaths chargeable to it. The prophylactic value of prompt recognition of this condition followed by immediate and adequate therapy cannot be overstressed. In pharyngeal and nasopharyngeal diphtheria the absorption of toxin is rapid because of the large vascular bed at the site of the membrane. Nevertheless, if adequate doses of antitoxin are given early the fatality rate is low; otherwise it increases rapidly unless other measures are used.

Most workers classify circulatory failure into two groups, early and late. Early circulatory failure is an essential part of the diphtheritic toxemia while late circulatory failure is a complication occurring during convalescence, in the stage of local inflammatory reaction of regeneration and repair.^{4,6,8,9,11}

During recent years,² following the work of Hoyne⁷ and Gordon⁶ we have been able to prevent and to reduce the mortality of diphtheritic myocarditis. Prophylactically, dextrose is administered intravenously without waiting for physical signs to appear; insulin is also administered to prevent the excessive spill-over and to facilitate the assimilation of dextrose. In 1927 Gordon first used dextrose routinely in early toxic diphtheria and was followed by Toomey¹⁰ in 1928. Early in 1934 Hoyne gave it routinely to all patients in the following groups: "1, those ill more than 3 days prior to receiving antitoxin; 2, 'bull neck' type regardless of which day the antitoxin had been injected; 3, patients with marked albuminuria; 4, all post-nasal cases and all malignant types of any character." His fatality rate was reduced to 9.8% from the usual 30 to 60%.

Treatment in late circulatory failure differs from that of early circulatory failure because the mechanism of failure is different. In addition to the myocarditis, involvement of the peripheral vasomotor mechanism has been demonstrated. In solving this problem the rationale of Dr. Gordon has been followed. The pressor principle of pituitary extract is used to restore and maintain blood pressure adequate for efficient circulatory function. It is imperative that the patient be well hydrated before the pitressin is given to avoid the undesirable reactions of shock, emesis, pallor and blanching of the skin. One-fourth to 1 cc. of pitressin is given subcutaneously every 8 hours, or oftener if indicated. Blood pressure readings are taken every 5 to 15 minutes until the blood pressure has returned to normal limits for the individual. Treatment must be continued until such normal blood pressure is reached, which may take a period of days and demands a knowledge of the normal blood pressure of small children. At variable intervals after pitressin has been given a compensatory diuresis occurs. It then becomes necessary to rehydrate the patient and repeat the pitressin. Each case must be strictly individualized and never become routine in its handling. Recently we have also used adrenal cortex (eschatin) in doses of

10 to 20 cc. to maintain blood pressure. Drugs such as caffeine-sodium-benzoate and adrenalin are not effective.³ Digitalis is contraindicated and its use is strongly condemned; it increases toxicity rapidly.⁵

During the year 1937 electrocardiograms were taken on all cases of diphtheria whenever possible. This was usually done between the tenth and fourteenth days of the disease. During 1938-1940 electrocardiograms were taken only in those cases showing pulse irregularity or clinical evidence of myocarditis. In this series there were 278 cases in which electrocardiograms were taken. Changes giving evidence of myocardial damage were found in 29 cases (10%). The abnormalities and lesions are tabulated in Table 3. Fifty per cent of the total deaths showed evidence of myocarditis clinically or at autopsy. In this group of 18 deaths bronchopneumonia occurred 11 times, "bull neck" 12 times, and tracheotomy had been needed 11 times.

TABLE 3.—VARIATIONS IN ELECTROCARDIOGRAPHIC RECORDINGS IN 279 CASES OF CLINICAL DIPHTHERIA.

	No. of cases.
Myocardial damage	29
Rhythm:	
Nodal	2
S-A	118
S-T	103
Aur. extrasystoles	1
Vent. extrasystoles	2
Shifting pacemaker	1
Axis deviation:	
Left	37
R+	55
None	187
Incr. pr. interval	3
Incr. intravent. cond.	4
Slurring QRS (2 or more)	29
Low voltage QRS (2 or more)	41
T wave changes:	
Flat T ₁	10
Flat T ₂	9
Inverted T ₁	4
Inverted T ₂	4
Diphase T ₁	0
Diphase T ₂	2
S-T interval deviations	8
Total	279

A case history is offered as an example of therapy just discussed in a patient showing evidence of marked toxemia, myocardial damage as demonstrated by electrocardiograms, and marked peripheral vasomotor collapse. Cases showing bundle branch block are fatal in a large percentage of those reported.

Case History. C. E. W., female, Caucasian, age 6 years, onset of illness was 2 days before admission, December 10, with fever, sore throat, and

dysphagia. A positive throat culture for diphtheria was obtained the day before admission. The patient was a well-developed and well-nourished child, flushed, toxic, acutely ill. Temperature was 101.4° , pulse 140, and respirations 24. There was a tender, non-fluctuating indurated swelling, lemon-size, extending from the left submaxillary region to the mastoid. The throat showed marked edema and swelling particularly on the left, the uvula being pushed to the right. Membrane covered this area and extended to the soft palate and right tonsil. The pharynx was obstructed by swelling and mucus. No respiratory distress was apparent. The lungs were clear, the heart normal, and the remainder of the examination negative.

The laboratory reported positive smears and cultures for Klebs-Loeffler bacilli. The blood count was not remarkable, and the urine normal except for albumin present on three occasions. A Roentgen Ray examination on January 16 showed the heart within normal limits, and no evidence of parenchymal infiltration.

Following negative skin tests, 10,000 units of diphtheria antitoxin were given intravenously and 30,000 units intramuscularly. During the first 2 weeks in the hospital the patient received daily 1000 cc. of 5% glucose intravenously covered by adequate insulin. On December 15 and 16 a slight drop in blood pressure was noted (82/53). The heart tones, however, were regular and of good quality. On December 17 there was a rapid progressive drop in blood pressure (50/?), marked pallor of the face, abdominal pain, weak pulse, and general evidence of circulatory collapse. Eschatin, pitressin, and 10% glucose intravenously were given with gradual improvement during the following 2 or 3 days.

Serial electrocardiograms were taken as illustrated in Figures 1 and 2.

These electrocardiograms were chosen from the series as demonstrating significant serial changes. Clinically, occasional dropped beats, extrasystoles, and a soft apical murmur were noted. The patient was discharged on March 11 as cured, and advised to continue with moderate rest.

Bronchopneumonia. Bronchopneumonia was reported in 80 cases. Terminally, it was present in 12 postmortem examinations and reported clinically in 8 other deaths. In recent years it has responded readily to the sulfonamide drugs.

Asphyxia and Stenosis. Infection limited to the larynx and below it becomes primarily a problem of asphyxia from mechanical obstruction rather than toxemia. The use of the bronchoscope and aspiration of the membrane through it or through the tracheotomy tube was instituted under the supervision of our consultant, Dr. Alden Miller. This procedure has reduced the fatality rate from asphyxia to 11% of the 36 deaths. These cases are never placed with lowered head, a mistake we formerly made.

Fifty-four cases required interference of some sort for obstruction of the airway. Aspiration of the membrane gave 1 case adequate relief. Intubation, done once or twice, relieved 5 cases but was unsatisfactory in 8 others. Tracheotomy was usually performed as a matter of choice, either because the tube to be used was too small or the inflammation and edema of tissue would quickly obstruct the tube's opening. Of a total of 48 who had required tracheotomy, 22 died. Of the fatal cases, 11 were of the "bull neck" type, 4 were laryngotracheal, and the remaining 7 had tonsillopharyngeal and laryngeal involvement.

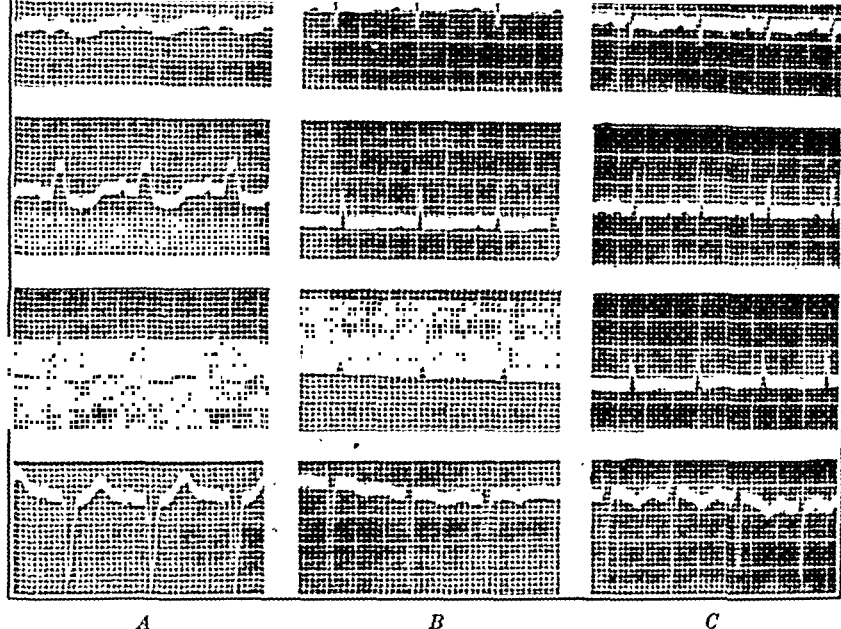


FIG. 1.—*A*, December 16, 8 days after onset, shows marked myocardial damage with bundle branch block of unclassified type. *B*, December 20: the bundle branch block has disappeared. Persistent evidence of myocardial damage as demonstrated by inverted T_1 , low voltage T_2 , and very small R , IVF. *C*, January 8, shows additional changes with presence of diphasic T_1 , T_2 , and the presence of R , I and R , IVF with increased elevation.

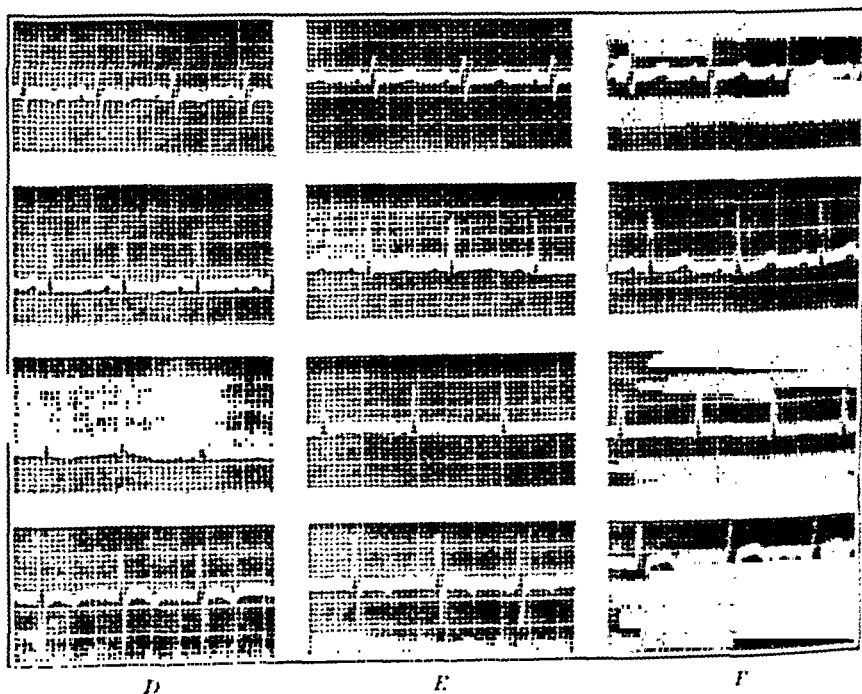


FIG. 2.—*D*, January 20, shows further elevation of R , I and R , IVF. *E*, January 28, shows a return of T_1 and T_2 to the upright position simulating a normal electrocardiogram. *F*, March 3, an essentially normal electrocardiogram.

Dr. S. Jesberg and Dr. A. Miller (Eye and Ear Hospital) from 1922 to 1927 have seen 6000 cases of which 503 were laryngeal. Of these, 25% died during the first 24 hours; and of the survivors, 22 ended in laryngeal stenosis of such degree as to demand more or less protracted treatment. In our series 5 patients had to have such treatment. Including these and others referred to them, Drs. Jesberg and Miller have treated 103 such cases with the following results: 6 deaths, 1 each from pneumonia, heart failure and lung abscess, and 3 of unknown causes; 9 still under treatment as of May 22, 1941, all greatly improved; 41 cured within 3 months; 13 cured within 6 months; 5 cured within 1 year; and 13 cured within 5 or more years. Most of these patients were treated by constant dilatation of the larynx by means of a section or core cut from an ordinary rubber urethral catheter pulled up into the introducer. These rubber sections were left in place for 2 or 3 weeks and replaced by larger ones. This method differs from other methods of indwelling dilators in that the cores are simply pieces of rubber catheters which may usually be introduced through the tracheotomy wound without making a large trough.

In 17 patients the stenosis was so great that before the dilators could be used and external tracheolaryngostomy had to be performed, in which the tracheotomy wound was extended to the upper limits of the stenosis, the scar tissue removed, and a trough formed by suturing the skin edges to the mucous membrane margins of the trachea. In 13 patients puncture cautery of the stenotic ring was done through the direct laryngoscope before the dilatations were begun.

Serum Reactions and Serum Sickness. There was 1 serum fatality noted in the 753 cases. The patient was 5 months old. Following a negative skin test, 20,000 units of antitoxin was given intramuscularly, at which time the temperature was 100.4° . Within 12 hours the temperature had risen to 106° , and the child died in 36 hours with a terminal temperature of 107° . Except for scant terminal bronchopneumonia there were no other complications. Unfortunately, permission for autopsy could not be obtained and the case was classified as probable serum reaction.

There were 181 cases (31.7%) out of 572 in which presence of serum sickness was noted; in 181 cases the record was incomplete in this respect. Fever, urticaria and serum arthritis were accepted as evidence of serum sickness. Table 4 shows the distribution by day of occurrence. The duration of reaction was 1 to 4 days and except for discomfort it presented no problem.

Miscellaneous Complications. The only other complication which occurred with any noticeable frequency was otitis media (15 cases). Pharyngeal paralysis which is reported so frequently in other hospitals⁶ occurred in only 7 of the 753 cases, and 1 case of peripheral paralysis was noted. It is probable that cases of the latter type do not return to contagious disease wards, but are seen elsewhere.

The disease most commonly seen with diphtheria is scarlet fever, of which we saw 24 cases. In the children's ward of the tuberculosis unit there have been outbreaks of diphtheria, often starting from an indolent case of the nasal type. Interestingly enough, the University of California Department of Hygiene reports¹ that the cultures from this group were classified as of the gravis type.

TABLE 4.—INCIDENCE OF SERUM SICKNESS AMONG 635 CASES BY DAY OF ONSET OF REACTION.

Days.	Cases.	Days.	Cases.
1	13	13	1
2	20	14	4
3	5	15	0
4	8	16	2
5	15	17	0
6	18	18	2
7	22	19	0
8	22	20	0
9	22	21	1
10	11	27	1
11	9	Unk.	1
12	4		
		Total	181

Death and Its Associated Conditions. Of the 36 deaths, 22 were in cases which had required tracheotomy, but of these only 4 were due to the laryngotracheo-bronchial type. Death in 1 case was due to hemorrhage following accidental severing of an anomalous carotid artery. Twenty deaths were in cases of the "bull neck" type. Table 5 shows the more common forms of complications and related conditions seen in the 36 cases of fatal diphtheria.

TABLE 5.—COMPLICATIONS AMONG 36 DEATHS OF DIPHTHERIA.

	No. of cases
Bronchopneumonia	20
Toxic myocarditis, clinical and autopsy	18
Toxic purpura	5
Atelectasis	3
Emphysema:	
Subcutaneous	3
Mediastinal	1
Otitis media	2
Hemorrhagic nephritis	1

Autopsies were performed on 17 of the 36 deaths. The chief findings other than those of diphtheria *per se* were: bronchopneumonia in 12, myocarditis in 9, atelectasis in 4, otitis media, toxic nephritis and adrenal hemorrhage each in 2 and hemorrhagic nephritis in 1. The myocardial lesions found differed in no essential from those reported by Warthin,¹¹ and were described as varying degrees and combinations of cloudy swelling, mononuclear infiltration, fragmentation of muscle, parenchymatous degeneration and necrosis, polymorphonuclear infiltration and fibrosis.

Summary. 1. Of 753 cases of diphtheria, 36 (4.8%) died.

2. Males represented 48% and females 52%.

3. The age incidence is charted, showing 61% before 10 years.
4. Average duration of illness before antitoxin was given was 3.7 days. Greater duration is shown to increase hazard.
5. Distribution of lesions and increased mortality with greater extension are tabulated.
6. Dosage of antitoxin was 20,000, 30,000 and 40,000 units in 28% each of the total, with lesser and larger amounts in a few cases, given intramuscularly except to the very toxic.
7. Therapy as used in the Communicable Disease Unit of the Los Angeles County General Hospital is discussed.
8. Complications of myocarditis, bronchopneumonia, asphyxia and stenosis, and other miscellaneous conditions are considered and treatment outlined.
9. Summary of deaths and the associated conditions is presented.

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THE EFFECT OF KIDNEY POSITION ON RENAL BLOODFLOW AND FUNCTION.

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THE piezometric* angle of the renal artery, as a factor determining renal bloodflow, was investigated. The importance of such angles in the regulation of arterial flow in other parts of the body has been emphasized by Swindle.⁷

Figure 1 shows how the renal circulation may be altered by changing the piezometric angle of the renal artery. With the renal artery elevated to Position A, the head pressure falls. At Position C the pressure increases instead.

* A piezometric angle is the angle between a tributary and the advancing blood stream in the mother artery.

The problem was approached in two ways: 1, pressure recordings were obtained from the cannulated renal artery of a dog while this vessel was made to form various angles with the aorta. 2, Diodrast clearance tests were done on several dogs with the renal artery at various angles.

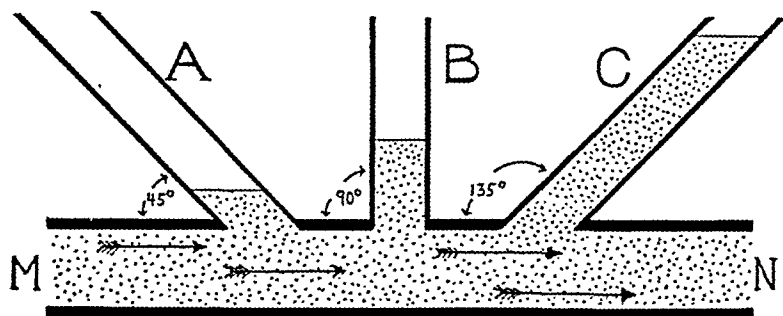


FIG. 1.—Pressure relationships in a system of tubes where the branches, A, B and C, form various angles with the main tube, MN, and fluid is traveling in the direction indicated. If B represents the approximate angle that the renal artery forms with the aorta, MN, and if the angle be changed to that of A or C, then the resultant head pressure of the renal artery will change as illustrated.

Methods. Seven dogs under nembutal anesthesia were used in this study. On the first dog, the right renal artery was cannulated and was connected with rubber tubing to a recording tambour. A 4% solution of sodium citrate was used as an anticoagulant. Tracings were obtained for various piezometric angles (Fig. 2). On the remaining animals a subcostal incision was made, so that the kidney could be exposed and ligated at the pedicle, including artery, vein, and ureter. The wound was then closed immediately to conserve body heat. Then, through a similar incision on the opposite side, the left kidney was exposed and the ureter was cannulated. An infusion of 1% Diodrast in physiologic saline was introduced at the rate of 20 drops per minute through a catheter inserted in an external jugular vein. For two periods of 60 minutes each urine was collected at 10-minute intervals and blood specimens were taken at the exact midpoint of each collection period. On Dogs 2, 3, 4 and 5 the kidney was unaltered in position during the first 60-minute period but during the second 60-minute period it was moved cephalad and held securely in this position by light packing. Precautions were taken to prevent compression of the renal artery, vein, and ureter. The angular change of the renal vessels was approximately 45 degrees. The procedure was reversed on Dogs 6 and 7. The kidney was elevated during the first period, and during the second period its normal position was restored. Systemic arterial blood pressures were taken several times during each experiment. Blood and urine were analyzed for iodine according to the method described recently by Alpert.¹

Results. Figure 2 illustrates that a considerable reduction of the mean blood pressure and also of the pulse pressure occurred when the piezometric angle of the renal artery was relatively acute. Similarly Table 1 presents evidence that the plasma clearance averaged 35.6% less with the kidney elevated, and Table 2 shows that an almost identical reduction (30%) occurred when the figures, corrected to surface area, are compared with those of the control periods of the

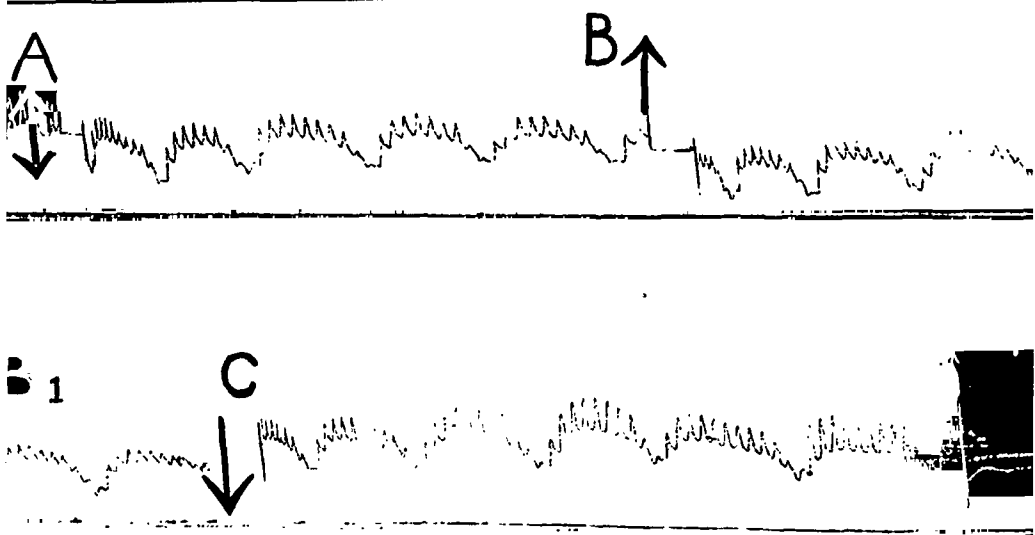


FIG. 2.—Effect on the mean blood pressure and the pulse pressure of the renal artery, when its piezometric angle is altered. A, with the renal artery at its normal position; B, with the renal artery elevated; B₁, continuation of B; C, with the renal artery lowered. The base line is a straight one and simply serves for comparison. Note that the mean and pulse pressures are reduced when the kidney is elevated and increased when the artery is lowered.

TABLE 1.—RESULTS OF DIODRAST CLEARANCE TESTS WITH THE KIDNEY IN (a) NORMAL AND (b) ELEVATED POSITION.

Each plasma clearance value is derived from a 1-hour test consisting of 6 urine collection periods of 10 minutes each, as described under Methods. The control period during which the kidney was in its normal position is indicated by (a) and the 60-minute period during which the kidney was elevated by (b).

Dog.	Weight (kg.).	Hematocrit (% cells).	Blood pressure (mm. Hg.).		Plasma clearance (cc./min.).	Corrected to sq. m.	Reduction (%).
2	11.4	48.6	98	(a)	91.4	163.2	
		47.5	104	(b)	54.9	98.0	39.9
3	12.0	52.5	106	(a)	98.8	167.4	
		53.2	98	(b)	62.8	106.4	36.4
4	5.9	49.3	86	(a)	57.9	156.5	
		47.5	90	(b)	38.2	103.3	36.4
5	2.8	54.0	82	(a)	29.8	141.9	
		51.5	84	(b)	20.2	96.1	32.3
Average							35.6

TABLE 2.—RESULTS OF DIODRAST CLEARANCE TESTS WHERE THE PERIOD OF KIDNEY ELEVATION PRECEDES THE PERIOD DURING WHICH THE KIDNEY WAS RESTORED TO ITS NORMAL POSITION. (a) AND (b) SIGNIFY THE SAME AS IN TABLE 1.

Dog.	Weight (kg.).	Hematocrit (% cells).	Blood pressure (mm. Hg.).		Plasma clearance (cc./min.).	Corrected to sq. m.	% improvement.
6	14.9	44.0	110	(b)	75.2	110.6	
		42.5	104	(a)	94.8	139.4	26.0
7	22.0	44.0	118	(b)	96.2	109.3	
		43.5	110	(a)	112.5	127.8	16.9
Average							21.4

first group of dogs. However, in the second group an improvement of only 21.4% resulted when the kidney position was restored. In this regard, the observation was made in all cases that the kidney became markedly congested and increased in size shortly after it was elevated.

It will be noted that the volume output of urine in Dogs 3, 4 and 5 was reduced from 0% to 51.9% after kidney elevation (Table 3).

TABLE 3.—ILLUSTRATES THE EXACT QUANTITY OF URINE ELABORATED BY EACH DOG DURING EACH 10-MINUTE PERIOD OF THE ENTIRE EXPERIMENT.

The figures in italics represent the period during which the kidney was elevated.

Time (min.).	Urine volume in cubic centimeters.					
	2.	3.	4.	5.	6.	7.
0						
10	3.4	5.8	6.6	8.2	<i>3.8</i>	<i>4.2</i>
20	3.6	6.0	7.4	8.0	<i>3.3</i>	<i>3.9</i>
30	4.0	7.4	8.6	8.2	<i>3.1</i>	<i>3.7</i>
40	3.8	5.8	8.0	8.4	<i>3.0</i>	<i>3.2</i>
50	3.9	6.0	9.1	7.2	<i>2.9</i>	<i>3.1</i>
60	3.8	5.6	8.1	6.8	<i>2.4</i>	<i>2.8</i>
	<hr/> 22.5	<hr/> 36.6	<hr/> 47.8	<hr/> 46.8	<hr/> 18.5	<hr/> 20.9
<i>Interval During Which Piezometric Angle Was Changed.</i>						
80						
90	4.8	3.4	6.5	4.2	3.8	3.1
100	4.3	3.2	6.9	4.2	3.9	3.0
110	3.8	3.4	6.6	4.3	4.4	3.2
120	3.8	3.0	6.3	3.9	4.0	2.8
130	3.4	3.3	5.7	3.3	4.6	2.4
140	3.0	3.2	5.3	2.6	3.7	3.2
	<hr/> 23.1	<hr/> 19.5	<hr/> 37.3	<hr/> 22.5	<hr/> 24.4	<hr/> 17.7

Comparable reductions did not occur in any of the other animals except Dog 6, but the urine output nevertheless diminished progressively during the elevation period in all of the dogs.

Discussion. It has been demonstrated in this investigation that renal bloodflow can be reduced considerably by elevating the kidney. The mechanism responsible is undoubtedly a simultaneous reduction of the mean blood pressure and also the pulse pressure. Friedman, Sugarman and Selzer³ state that a reduction of both mean and pulse pressure is invariably followed by renal vasodilatation and a fall in the glomerular filtration rate. It can be safely assumed, therefore, that glomerular filtration in these dogs was also reduced. That this occurred is further substantiated by microscopic sections which reveal that the glomerular capillaries of elevated kidneys appear considerably less filled with blood than those of normal, control kidneys.

Before results of this nature may be applied clinically, it is necessary to establish that the kidney of human beings is not fixed and identical in position in all individuals. Moody and Van Nuy's² claim that the kidneys in most healthy men and women have a con-

siderable range of mobility, the range of excursion in women varying between 0.1 to 9.3 cm. They conclude that the kidney is definitely a floating organ. Acknowledging, therefore, that variability of position exists, it is obvious that there is also variability of the piezometric angles of the renal artery. This may well be an anatomic basis of what is commonly spoken of as "a predisposition toward hypertension."

Woodruff and Milbert⁸ have demonstrated that kidney position is altered by pregnancy and that as gestation progresses, the kidney is gradually raised cephalad by the advancing uterus. Therefore, the distinct change in renal bloodflow which follows when the piezometric angle of the renal artery is reduced may be the factor which initiates the clinical picture of toxemia of pregnancy. Since the degree of renal embarrassment depends on the height to which the kidney is raised, there are factors present in the incidence of toxemia which indicate that in such cases the kidney may be elevated relatively higher than in otherwise normal pregnancies. For instance, Stander⁶ notes that toxemia is more frequent in primiparæ rather than in multiparæ and the uterus is commonly overdistended as with multiple pregnancy or even polyhydramnios. Interesting in regard to the observation that primiparæ are more susceptible is the notation by Griefenstein⁴ that recurrences in previously eclamptic women average only 2.6%. It is possible to explain these apparently unrelated facts on a physiologic basis. Primiparæ unquestionably have greater tone to their abdominal musculature, they therefore carry their pregnancy relatively high and the pressure displacing the kidneys is conceivably greater. On the other hand, multiparæ with their relaxed abdominal musculature permit greater forward protrusion of the pregnancy with a consequent diversion of the otherwise cephalad pressure. In addition, the presence of an overdistended uterus still further contributes to the displacement of the kidneys.

Corcoran and Page² in their study of renal function in late toxemia of pregnancy discovered that those cases uncomplicated by previous hypertension have without exception a low filtration rate even in the presence of a normal or decreased total renal bloodflow. They concluded by a process of elimination that the primary cause of the diminished filtration rate is increased resistance of the glomerular filter. In view of the fact that the hydrostatic pressure of the glomerulus can be reduced so markedly by elevation of the kidney it would appear more correct to assume that derangement of the glomerular function occurs secondarily.

Summary. 1. Renal bloodflow is profoundly reduced when the piezometric angle of the renal artery is made relatively acute.

2. It is possible that the anatomic basis of predisposition toward hypertension lies in the extreme variability of the position of the kidney.

3. The deranged renal function of uncomplicated late toxemia of

pregnancy may be the result of relatively high elevation of the kidney during gestation, depending on body type and abdominal muscle tone.

Acknowledgment is made to Dr. Eben J. Carey, Dean and Director of the Department of Anatomy at Marquette University Medical School, for providing the facilities and material which made this investigation possible; to Dr. P. F. Swindle, Professor of Physiology, for his many valuable suggestions; to Dr. J. C. Grill, Associate Professor of Pathology and Bacteriology, for examining the microscopic sections. Gratitude is also expressed to Mr. E. Haushalter for his assistance in the operative procedure.

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GIANT FOLLICULAR LYMPHOBLASTOMA (GIANT LYMPH FOLLICLE HYPERPLASIA).*

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SINCE 1925, when Brill, Baehr and Rosenthal⁶ first called attention to the pathologic picture now generally referred to as giant follicular lymphoblastoma, a number of reports have appeared in the literature dealing with this condition. More recently there have been several excellent publications in which the discussions of the clinical and pathologic aspects were based on large series of cases. The purpose of this report is to stress certain points in connection with this disease entity rather than to add to the ever-growing number of cases.

We feel that, although the condition is well known to and easily recognized by most pathologists, it is still thought of only too rarely by the clinician. The importance of its early recognition—and this can be done only by biopsy and histologic study of the lymph node removed—becomes apparent when one knows how remarkably radiosensitive these tissues are, particularly in their early stages. However, it must be borne in mind that recurrences are

* Presented in part before the Eastern Medical Society of the City of New York on December 27, 1940.

common and that after a number of years the disease may take a malignant form and terminate as lymphosarcoma, lymphatic leukemia or Hodgkin's disease.

Definition. Giant follicular lymphoblastoma is a relatively benign disease of the lymphatic system. It is characterized by: lymphadenopathy, which is due to enlargement of the follicles of the involved nodes; splenomegaly in most cases; a normal blood picture; the absence of anemia and cachexia; a long course; and a prompt response of the lymph nodes and spleen to Roentgen ray therapy in the early stages of the disease.

History. In 1901 a case of "simple hyperplasia" of lymph nodes was reported by Becker⁵ which apparently showed the histologic picture of the disease entity under consideration. In the next 20 years a few other investigators^{7,8,12} described the condition. However, it was not until Brill and his coworkers reported their 2 cases in 1925 that the attention of the medical profession in this country was drawn to this disease. They considered it a benign lymphadenopathy and applied the name, "giant follicle hyperplasia." Two years later Symmers^{14a} reported 3 additional cases. In that same year Baehr and Rosenthal² reported a total of 6 cases, but now described the condition as "malignant lymph follicle hyperplasia of spleen and lymph nodes." They regarded it as a clinical and pathologic entity distinct from lymphosarcoma.

By 1931, Baehr, Klemperer and Rosenthal³ were convinced that the disease could be differentiated from simple follicular hyperplasia of inflammatory nature. Furthermore, they had followed some of their cases long enough to observe that later in the course of the disease, the follicles fused, the capsule became infiltrated and the surrounding tissue invaded. This forced them to the conclusion that the condition was a form of lymphosarcoma. They therefore proposed the name "follicular lymphoblastoma," which is now in fairly general use. The above-named group continues to maintain this view.¹

The inflammatory or toxic origin of the disease has been championed by Symmers^{14b} who, in 1938, reviewed 32 cases, and applied the term "giant follicular lymphadenopathy with or without splenomegaly."

Thirteen seen cases and 59 collected from the literature were studied (1940) by Baggenstoss and Heck.⁴ More recently, Gall, Morrison and Scott⁹ reviewed 63 cases diagnosed by biopsy or necropsy.

Pathology. Our purpose is to deal with the clinical aspects of the disease and its pathogenesis. In order to clarify our views we shall discuss briefly the pathologic changes encountered. The disease appears to have a multicentric origin, so that enlarged lymph nodes may be found in various parts of the body. These may attain great size, the nodes remaining discrete and firm in consistency. Gener-

ally the spleen is markedly enlarged. Involvement of various other organs has been reported. As the reported cases accumulate it becomes evident that lymphatic tissue of almost any organ in the body may be the seat of such lesions.

The enlargement of the lymph nodes is due to a marked increase in the number and size of the lymph follicles. These are usually diffusely scattered throughout the node and may reach tremendous size. As the disease progresses the follicles may fuse and the histologic picture change so completely that no trace of the follicular structure may be found.

Similarly, the splenic enlargement is due to an increase in the number and size of the Malpighian corpuscles. When perinodal tissue is involved, the same follicular arrangement is seen as within the nodes themselves.

The primary change within the lymph follicles themselves appears to be the formation of large "germinal centers" surrounded by a rim of darker staining adult lymphocytes. The enlargement of the follicles and their increase in number causes compression of the interfollicular structures. Gall and his associates recognize four types of lesions, dependent largely upon the state of preservation of the follicles, and express the view that they probably represent progressive phases in the pathogenesis of the disease.

Clinical Course. As in most diseases of the lymphatic system, so in giant follicular lymphoblastoma the clinical picture is very variable. The disease usually makes its appearance in the third or fourth decade of life. The first manifestation is generally an enlargement of regional lymph nodes, axillary, inguinal, cervical, retroperitoneal, and so on. The involvement may be more or less generalized when the patient first comes under observation. Splenomegaly occurs in a fair percentage of cases, variously given as 33% to 61.1%.

It is remarkable that the patient has a feeling of well-being even when the lymphadenopathy is widespread. Cachexia is usually absent and anemia a relatively rare occurrence. In the early stages the blood picture may be entirely normal. The disease runs a protracted course. The average duration is 5 to 6 years. Two cases referred to by Baggenstoss and Heck were alive after 17 years. Ascites and hydrothorax are not infrequently encountered. Osseous, cutaneous, pulmonary, genito-urinary, gastro-intestinal and tonsillar involvement have been reported.

All investigators agree that in the early stages of the disease the lymph nodes show a remarkable sensitivity to the Roentgen rays. The lymph nodes may no longer be palpable and the spleen may be restored to its normal size after a few exposures. However, as the disease progresses, this radiosensitivity diminishes and finally there is no response to Roentgen ray therapy. After repeated remissions, the disease may terminate as lymphosarcoma, lymphatic leukemia

or Hodgkin's disease. Thus far, no cases have been reported as cured.

Case Reports. Two cases seen by us are briefly summarized here to illustrate the early clinical manifestations.

CASE 1. Mrs. B. R., aged 57, was admitted to the Medical Service of the Beth Israel Hospital on February 13, 1940, complaining of fatigue of 1 month's duration and pain in the left leg for 1 week. During the 3 years prior to admission she had been examined repeatedly because of abdominal distress and eructations attributed to a proven cholelithiasis. She was examined 1 week before her admission to the hospital and found to have a mass in the abdomen. Her past history and family history were non-contributory.

On admission to the hospital her temperature was 99.6° but reached normal the next day and remained so. There was slight conjunctival icterus. A soft systolic murmur was heard at the apex. The lungs were clear. The superficial veins in the suprapubic region were somewhat distended. A huge mass filled the left side of the abdomen and flank, the medial border of the mass extending to the mid-line, the lower edge to the iliac crest. The mass moved somewhat on respiration and was ballotable. The edge of the spleen could be felt just below the costal margin and distinct from this tumor mass. The liver could not be palpated. One small non-tender node was present in the right supraclavicular region. Several discrete, non-tender lymph nodes were palpated in both inguinal regions. They were more numerous on the left side where one larger node, about $\frac{1}{2}$ inch in diameter, could be felt. From the vaginal examination it would appear that the abdominal mass did not arise from any of the pelvic organs. On digital rectal examination a firm, non-tender mass could be felt extrinsic to the rectum.

A blood count showed 4,500,000 red cells and 90% hemoglobin. There were 6400 white blood cells with a normal differential count including 3% eosinophils. The blood chemistry figures were normal. Blood Wassermann test was negative. Repeated urine examinations were negative except for occasional pus cells in non-centrifuged specimens. The stools showed no occult blood.

Roentgenologically, the colon was found to be normal in position and normal in contour except for diminution of the lumen of the descending portion. The gall bladder was long and flexible and contained numerous radio-opaque calculi. An intravenous pyelogram showed normal kidneys, pelves and calyces. There was evidence of extrinsic pressure on the upper surface of the bladder. On the flat film of the abdomen the liver appeared normal in size and the shadow of a small spleen could be seen very clearly. A large, moderately opaque mass occupied the greater portion of the left side of the abdomen. This mass did not displace the left kidney, nor encroach on the left psoas shadow. Roentgen rays of the chest showed no evidence of mediastinal involvement.

On February 26, 1940, a lymph node was removed from the left inguinal region. Microscopic examination of this node showed tremendous follicles resembling large "germinal centers" and surrounded by a zone of mature lymphocytes. In some places the sinusoids and lymphocytes were markedly compressed by the giant follicles (Fig. 1).

The patient received 9 Roentgen ray treatments in all. After the sixth exposure a definite and marked decrease in the size of the abdominal mass could be noted. At the time of her discharge from the hospital, on March 24, 1940, the abdominal mass was no longer palpable. A few very small lymph nodes persisted in her left inguinal region and one in the left supraclavicular region.

Up to the present time, February 1942, the patient has continued in good health and has shown no recurrence of the adenopathy.

CASE 2. Mrs. Y. S., aged 54, was admitted to the hospital on April 28, 1941, because of a slight painless swelling on the left side of the neck of 2 months' duration. There were no other complaints. There was nothing of note in her past or family history.

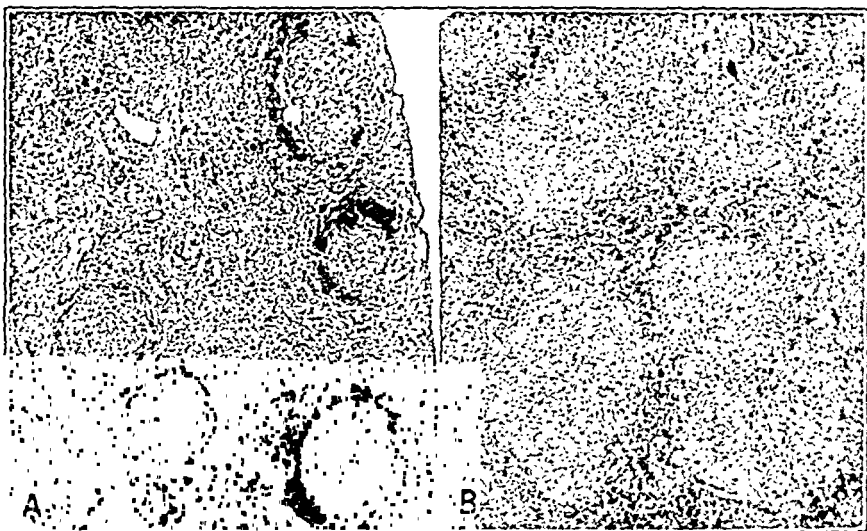


FIG. 1.—A, Section of a "normal" lymph node with large, pale staining centers surrounded by a rim of adult lymphocytes. The lymph follicles are distinctly separated. B, Markedly enlarged follicles with compression of the interfollicular structures (Case 1). (Same magnification as that used in A.)

On admission to the hospital she did not appear acutely or chronically ill. Her temperature was 100.6° , and subsequently ranged between 98.6° and 99.8° . A firm, non-tender, freely movable mass about $1\frac{1}{2}$ inches in diameter was present in the left posterior cervical region. This was not attached to the skin or the underlying structures. There were also a few small, discrete lymph nodes in the anterior triangle of the left side of the neck and 2 small nodes in each axilla. There was no other apparent adenopathy. The liver and spleen could not be palpated. The remainder of the physical examination was essentially normal.

Blood studies showed 4,550,000 red cells with 80% hemoglobin. The white cell count ranged from 3100 to 3300. There was a normal differential count with 3% to 4% eosinophils. Blood chemistry was normal. The blood Wassermann test was negative. Urines showed a heavy trace of albumin and many pus cells with occasional pus clumps.

Roentgen ray examination of the chest showed some calcified nodes in both hilar regions but no mediastinal involvement.

On May 3, 1941, a lymph node was removed from the left supraclavicular region. Microscopic examination of this node showed the early changes of giant follicular lymphoblastoma (Fig. 2).

The patient was discharged on May 9, 1941, and referred for Roentgen ray therapy. In all, she received 15 treatments, the last one on June 16, 1941. On June 9, 1941, it was noted that the size of the lymph nodes had

diminished. By June 16 the nodes in the right supraclavicular region were no longer palpable. When seen on November 14, the patient was generally well. There were no palpable cervical, axillary or inguinal nodes. The liver and spleen could not be palpated.



FIG. 2.—Tremendous enlargement of the follicles which are surrounded by darker staining, adult lymphocytes compressed into a thin rim. There is also fusion of the follicles at some points (Case 2).

Comments. Despite careful studies of biopsy and autopsy material there still exist differences of opinion as to the classification and pathogenesis of giant follicular lymphoblastoma. Most investigators agree that this condition represents merely a stage in the pathologic changes occurring in the lymphatic tissue, since sooner or later this relatively benign disease terminates as a lymphosarcoma, or lymphatic leukemia. A terminal picture of Hodgkin's disease has also been suggested by Symmers.^{14b}

It has been suggested by Ross¹³ that this condition is a hyperplasia of undifferentiated cells with unrestricted potentialities for differentiation. He regards it as a "lymphoid reticulosis." Jackson¹¹ also looks upon it as an early form of malignant lymphoma which may become transformed into any one of the recognized types. Symmers^{14b} maintains his original view that giant follicular lymphoblastoma is most likely of inflammatory or toxic origin. He feels it is "capable of direct transformation into a polymorphous cell sarcoma;" he holds that it may also have superimposed upon it the histologic features of Hodgkin's disease by the deposition in the modified lymph nodes of megakaryocytes from the bone marrow. In like fashion it may become associated with the changes of lymphatic leukemia. These views are at variance with those of Baehr

and Klemperer who state that their experiences suggest "that follicular lymphoblastoma may represent a borderline condition between lymphosarcoma and lymphatic leukemia, just as in its early stages the disease may seem to represent a transition between hyperplasia and lymphosarcoma."¹

It has long been recognized, and recently stressed by one of us,¹⁰ that in different diseases involving the lymphatic tissue different structural components of the lymph nodes are primarily involved. So, for example, we find that in Hodgkin's disease the endothelial portion is the seat of the disorder. There are other diseases of the lymphatic system in which the involvement is fundamentally one of the lymphocytic tissue of the lymph glands. Such is the case in lymphatic leukemia. In still others the lymphocytic and the reticular structures are involved, giving the pathologic picture of lymphosarcoma and reticulum cell sarcoma. In giant follicular lymphoblastoma the "germinal centers" of the secondary follicles are the point of departure of the pathologic process. In inflammatory diseases, such as tuberculosis and syphilis, all structures within the lymph nodes usually show changes.

It is generally true that the patient in whom a diagnosis of lymphosarcoma is established by biopsy will continue to have lymphosarcoma until his death. The same holds for Hodgkin's disease and lymphatic leukemia. Our concept is that in giant follicular lymphoblastoma the groundwork for the terminal picture is laid down early in the disease, despite the fact that in the very earliest stages this cannot at present be recognized by the pathologist.

We feel that, whatever the etiologic factor, the disease starts in the so-called "germinal centers" of the lymph follicles. At this stage it is still reversible, but it may terminate as lymphosarcoma, lymphatic leukemia or, in rare cases, Hodgkin's disease.*

A knowledge of the course the disease may take and the fatal termination which may be anticipated is of practical importance. It is possible that, by continuing Roentgen ray therapy during the periods of remission, the development of the malignant phase may be retarded or prevented.

Conclusions. 1. The pathologic changes encountered in giant follicular lymphoblastoma are described briefly.

2. The clinical course of the disease is outlined and 2 illustrative cases are cited.

3. The fact is stressed that the disease may terminate with the picture of lymphosarcoma, lymphatic leukemia or, rarely, Hodgkin's disease.

* We do not know personally of any well-authenticated cases of giant lymph follicle hyperplasia terminating in Hodgkin's disease; nor is it conceivable, except as coincidence, unless one accepts the cells that compose the pale centers of the follicles as identical with the endothelioid cells of Hodgkin's disease. The nature of the cells of the pale centers, to be sure, still remains in doubt.—HARRON'S NOTE.

4. The concept that the groundwork for the terminal picture is laid down in the very beginning of the disease is offered.

5. It is suggested that Roentgen ray therapy during the remissions in the course of the disease may retard or prevent the development of the malignant phase.

We wish to thank Dr. Alfred Plaut for the histologic preparations.

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ACUTE MYOCARDIAL INFARCTION WITHOUT DEVIATION OF THE S-T SEGMENT IN THE ELECTROCARDIOGRAM.*

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AMONG the deviations from the classical pattern in recent myocardial infarction^{2,4,7,11-13} we have found a type for which no proven explanation has been offered. It is the type which resembles the classical curve but lacks the characteristic sign which is part of the expected record, namely, an elevation of the S-T segment, the so-called "high take off" of the T-wave in the older literature.

The case presented in this report is the only one with autopsy in our series of 8 cases with recent myocardial infarction in which the acute stage showed no S-T deviations or only an S-T depression. This electrocardiogram in the autopsied case was found to be associated with recent infarction which did not extend to the epicardium. The explanation offered by Boyd and Scherf⁵ and by Ashman and Hull¹ thus seems to be substantiated.

* Aided by the A. D. Nast and the Emil and Fanny Wedeles Funds for Cardiac Research.

Case Report. A 63-year-old female was admitted to the Orthopedic Service (Dr. D. H. Levinthal) of this hospital on June 15, 1941 complaining of severe pain in the right hip joint. One hour before admission she had stumbled in her room at home, had fallen to the floor and was unable to rise. Several months before she had complained of pain in the right hip, and Roentgen-ray had revealed a cystic lesion of the neck of the right femur. A review of systems was essentially negative. The past history did not reveal any symptoms indicative of cardiovascular disease.

On admission the temperature was 98.6° F., the pulse 96 and regular, respiration 22, blood pressure 140/90 mm. Hg. Physical examination showed a normally developed and well nourished female, in evident severe pain. Heart, lungs and abdomen showed no abnormal findings. The right leg appeared shorter than the left. A Roentgen-ray picture revealed a pathologic fracture of the neck of the femur at the level of the lesser trochanter. Russel traction was applied, and morphine administered for pain. Laboratory findings: glucose 97 mg. per 100 cc., N.P.N. 38 mg. per 100 cc., uric acid 4.4 mg. per 100 cc., calcium 9.9 mg. per 100 cc., phosphorus 2.6 mg. per 100 cc., phosphatase 2.9 units. The blood count showed R.B.C. 4 million, W.B.C. 10,250 with 70% neutrophils. There was some albumin in the urine and a few granular casts were found on microscopic examination.

The Russel leg traction was not satisfactory, and so an attempt was made on June 24, 1941, to reduce the fracture under pentothal anesthesia, but the Roentgen-ray on the following day revealed the fragments still in poor position. Reduction was attempted again on June 28 with little success. The patient began running a low grade fever and on July 3 a diagnosis of bronchopneumonia was made and sulfathiazole therapy started. A chest film showed an area of haziness adjacent to the apex of the heart. An electrocardiogram (Fig. 1A) was taken. On July 7 the Roentgen-ray revealed the pneumonic process to be resolving. Aspiration biopsy from the fracture site showed blood inflammatory cells and occasional giant cells. On July 15 curettement of the bone cyst was carried out under gas anesthesia. A Smith-Peterson nail was introduced to unite the bone fragments. The immediate postoperative condition was excellent.

Suddenly, on July 17, the temperature rose to 102° F., the pulse to 120, the patient became markedly dyspneic and cyanotic, the blood pressure dropped to 85/55 mm. Hg., and the W.B.C.'s rose to 20,000. The R.B.C.'s had fallen to 2,700,000. Signs of bilateral bronchopneumonia were present. The patient received 50 cc. of 5% sodium sulfathiazole intravenously and 2000 cc. of glucose and saline by clysis.

On July 18 the condition appeared unchanged; temperature 103.6° F. A transfusion of 250 cc. of blood was administered, followed by 1000 cc. of 2.5% glucose.

On July 19 an electrocardiogram was taken (Fig. 1B). The blood pressure then was 82/70 mm. Hg. A blood transfusion of 250 cc. was repeated and 2000 cc. of 5% glucose were given by venoclysis.

On July 20 the patient's condition was "almost terminal." Cheyne-Stokes breathing, marked cyanosis was present, the temperature was 103° F., the blood pressure 92/80 mm. Hg. Again, 500 cc. of blood and 2000 cc. of 5% glucose were given.

On July 21 the third electrocardiogram was taken (Fig. 1C). Another 500 cc. blood transfusion and 2000 of 10% glucose were administered. The patient died the following morning.

At no time during her hospital stay did she receive digitalis.

Autopsy Findings. Pathologic diagnosis: Myxomatous central osteochondroma of the right femur with subtrochanteric fracture; severe coronary arteriosclerosis and atheromatosis of the aorta; recent thrombus in the

anterior descending branch of the left coronary artery; recent myocardial infarct of the anterior wall of the left ventricle and interventricular septum; mural thrombi in the left ventricle; terminal endocarditis superimposed on an old endocarditis of the mitral valve; passive hyperemia of the liver; bilateral hydrothorax; acute purulent bronchitis; recent bronchopneumonia of the right upper lobe; fibrosis and passive hyperemia of the spleen; arteriosclerotic scars of the kidneys; foci of old encephalomalacia.

Gross examination of the heart: The heart weighs 225 gm. The epicardium appears normal. The left ventricle is soft. The mitral valve is thickened and shows a few minute glistening verrucae along the line of closure. The valve circumferences measure: tricuspid, 11 cm.; pulmonic, 7 cm.; aortic, 7 cm.; mitral, 8.8 cm. On section the myocardium of the anterior wall of the left ventricle and distal portion of the anterior septum shows large yellow patches sharply outlined against the remaining dark-brown muscle, especially towards the endocardial aspect (Fig. 2, A, B). They involve 0.5 to 0.75 cm. of the thickness of the myocardial wall and extend, in a vertical dimension, from about 1.5 cm. below the origin of the anterior descending coronary artery to the apex; horizontally, the anterior half of the septum and the medial 2 to 3 cm. of the anterior wall of the left ventricle are involved. The infarct comes closest to the epicardium in the anterior portion of the septum, becoming more subendocardial as it is followed laterally in the anterior ventricular wall. Friable grayish-pink mural thrombi adhere to the endocardium near the apex. The left ventricle is dilated and the ventricular wall measures 0.8 cm. in thickness. The right ventricular wall measures 0.2 cm. in thickness and shows fatty infiltration. The coronary ostia are patent; their lumina are narrowed by many yellow plaques. Proximal to an almost total arteriosclerotic occlusion of the left anterior descending is a gray-red slightly attached thrombus about 1 cm. distal from the origin of the artery. The right coronary is moderately narrowed.

Microscopically, there are large areas of deep-staining and granular myocardial fibers with faded or absent nuclei. In and around these areas are numerous neutrophils with an occasional extravasation of erythrocytes. Adherent to the endocardium are a few masses of recent thrombi containing some fibroblasts and a few capillaries. The infarcted areas appear in various sections to involve predominantly the inner half to two-thirds of the wall (Fig. 2C). Occasional small foci of necrotic fibers are seen at a distance of approximately one low-power field from the epicardial surface. The epicardial fat contains a loose scattering of monocytes.

Anterior descending coronary artery: The intima is markedly thickened by fibrous connective tissue containing many acicular spaces, foam cells and areas of calcification. The small lumen is filled by a recent laminated thrombus with a few invading fibroblasts.

Mitral valve: The valve is thickened by cellular fibrous connective tissue. On one aspect is a small patch of adherent fibrin, on the opposite aspect is a subendocardial area of loose fibrous tissue containing mononuclear cells.

Addendum. While this article was in press, a case similar to that reported above was observed in which a diagnosis of subendocardial infarction was made clinically on the basis of the electrocardiogram shown in Figure 3. This was confirmed at autopsy. The characteristic changes are shown in the chest leads. In the limb leads the possibility of a concordant type of left ventricular preponderance or of a transitory coronary insufficiency would have to be entertained. However, in view of the chest leads, the diagnosis of recent subendocardial myocardial infarction was favored.

Necropsy. The heart weighed 425 gm., the right auricle and ventricle were dilated and the left ventricle was hypertrophied. The endocardium

of the left ventricle was shaggy. In the inner two-thirds of the myocardium of the left ventricle, there was grayish-white streaking and stippling with pin-point hemorrhages, and the architecture was obscured. These changes involved the interventricular septum, and the anterior wall and the inferior aspect of the posterior wall. As in the first case, the architecture of the outer rim of the myocardium was apparently unaltered. The coronary arteries were moderately sclerotic, the anterior descending branch of the left coronary artery was completely occluded by a recent thrombus about 4 cm. from its point of origin.

Electrocardiogram. The first record (Fig. 1A) (taken on July 3, 1941) shows a regular sinus rhythm at a rate of 90. There is a left axis shift. The S-T segment is slightly depressed in Leads I and II, however, it is not below the level of the P-Q segment. T_1 and T_2 are upright, T_3 is small and inverted. Lead CF_2 is normal. CF_4 shows a slight depression of the S-T segment. The record was interpreted as probably within normal limits.

The second record (Fig. 1B) (taken on July 19, 1941) shows a sinus tachycardia with a rate of 120. There is a decrease in voltage both in the limb and chest leads. The QRS in CF_2 is now entirely inverted. The S-T segment is slightly elevated in CF_2 and no longer depressed in CF_4 . T is smaller in both chest leads. The electrical systole (QRST interval) is prolonged, measuring 0.34 sec. instead of the expected 0.27 ± 0.04 sec. The record was interpreted as suggestive of an atypical anterior wall infarction and a repeat record was requested within 48 hours. This interpretation was based entirely on the changes in CF_2 , since neither the limb leads nor the generally favored apical lead (in our case identical with CF_4) were suggestive of infarction.

The third record (Fig. 1C) was taken 2 days later (July 21, 1941) and 1 day before death. The heart rate is slower (100); there is some further decrease in voltage in the limb leads. S-T is now definitely depressed in Lead I and T_1 is almost isoelectric, T_2 is small and diphasic; T is smaller in CF_2 and is now inverted in CF_4 . These changes confirmed the impression of an atypical recent myocardial infarction.

Comment. It has been shown conclusively that elevation of the S-T segment in cases of pericarditis is due to involvement of the uppermost (nearest epicardium) layers of the myocardium.^{2,10} Recent experiments⁵ suggest that changes confined to the subendocardial layers are not reflected in the electrocardiogram in the same way as changes in the subepicardial layers,^{5,6} and that elevation of the S-T segment appears to be associated with involvement of the subepicardial myocardium only. In the light of these experimental findings, the question presents itself whether electrocardiograms in acute myocardial infarction with absence of S-T elevation are due to a peculiar location of the necrosis which leaves the subepicardial muscle free. [The accumulated knowledge about the separate layers of the ventricular musculature, with distinguishable electrocardio-

graphic patterns, blood supply and intramyocardial Purkinje fibers, now demands attention in any consideration of relationships between myocardial infarct and the electrocardiogram (see Robb and Robb: *AM. J. MED. SCI.*, 197, 7, 18, 1939, and Lowe, F. E.; *Am. Heart J.*, 21, 326, 1941). We know that the authors are aware of this knowledge, but as they have not considered it in their text, we wish to call attention to it here.—ED. NOTE.]

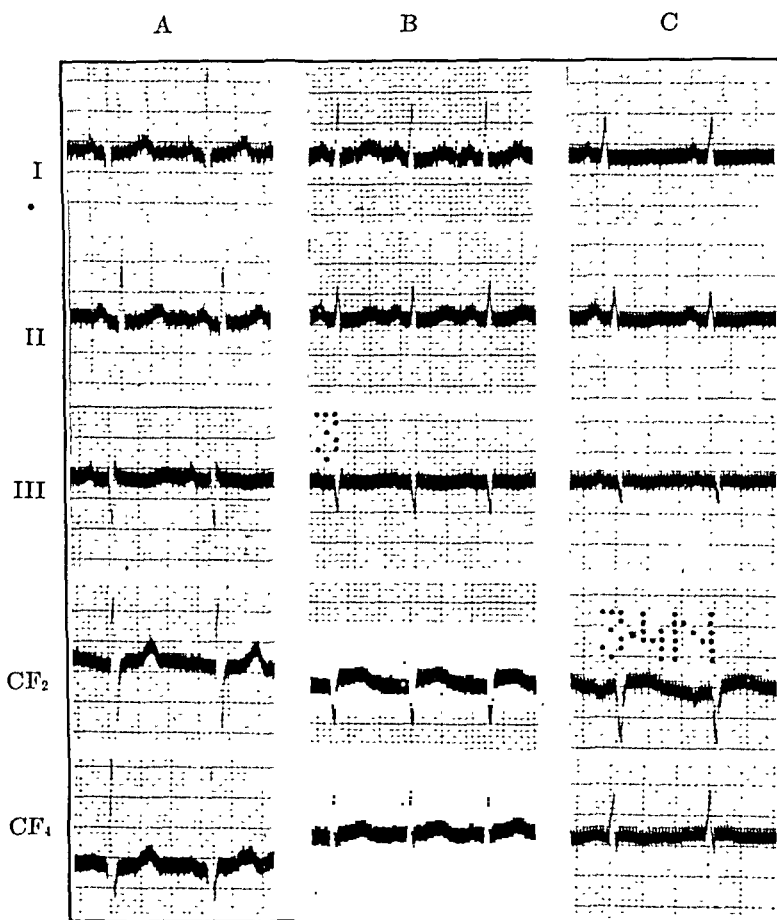


FIG. 1.—Five lead electrocardiograms of the patient. Record A, taken on July 3, 1941; B, on July 19; C, on July 21.

Gross and microscopic examination of the heart in our case showed a very recent infarct of the anterior wall of the left ventricle with predominant involvement of the subendocardial layers, the subepicardium being practically uninvolved. The infarct was considered typical in location and size for such located infarcts except for failure to extend to the epicardium.

According to the criteria of Mallory, White and Salcedo-Salgar⁸ the histologic findings of recent necrosis, neutrophilic infiltration predominantly interstitial but occasionally more diffuse; and only the rarest evidence of phagocytosis or new capillary or fibroblast

formation, together set the estimated ages of the various observed areas of the infarct between 2 and 5 days. These postmortem findings, therefore, correspond to the lesion postulated for this variety of atypical electrocardiogram.

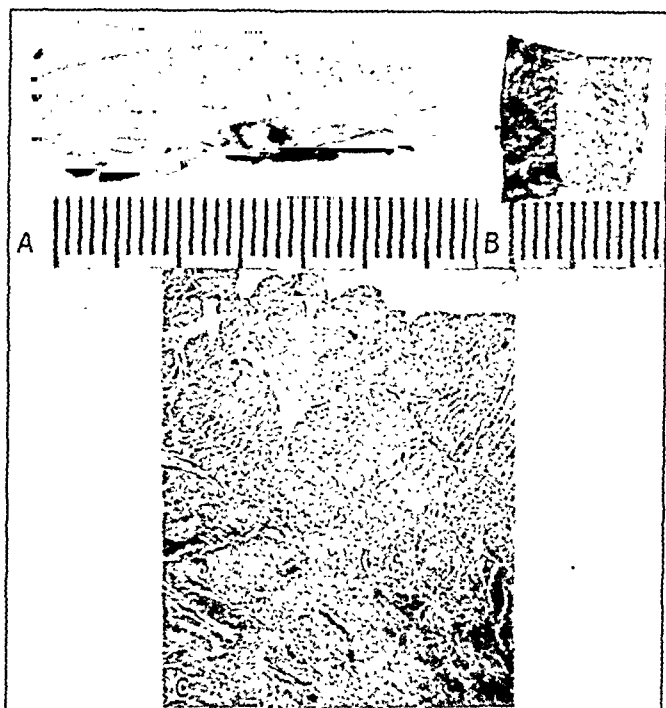


FIG. 2.—A, Section through unstained anterior wall of left ventricle. Note outer (upper) darker zone which indicates uninvolved myocardium and inner lighter zone indicating infarction. Note dark fragment of mural thrombus adherent to the endocardium (ruler in mm.). B, Section through anterior wall of left ventricle (Sudan IV preparation). Note deeply stained pericardial fat, mid-zone of uninvolved myocardium and subendocardial zone of infarction (ruler in mm.). C, Photomicrograph of section through anterior wall of left ventricle. Note layer of epicardial fat (faintly shown at very top of photograph), lighter staining uninvolved myocardium and darker stained zone of infarct. (Iron-hematoxylin and eosin, mag. 22.)

Of course, not every electrocardiogram of this type would be expected to reflect such peculiar location of the infarct, since there are several other factors which may account for the absence of the S-T elevation in the early stage of infarction. Thus, the acute S-T stage may be so transitory as to disappear before a record is taken. In other cases, the S-T elevation may be confined to the chest leads, with no evidence in the limb leads. One of the causes for this last is the coexistence of tendencies influencing the position of the S-T segment in opposite directions such as occurs especially in cases with left ventricular preponderance and anterior wall

infarction, or in infarction of the mixed anterior and posterior wall type.

Only after these factors have been excluded may a limb plus chest lead electrocardiogram without S-T elevation early in acute myocardial infarction be considered possibly to reflect infarction not extending to the epicardium.

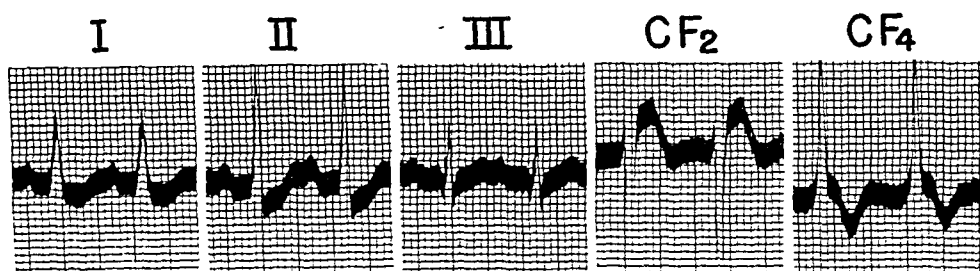


FIG. 3.—Five lead electrocardiogram of patient mentioned in addendum, taken 24 hours after the clinical attack and 24 hours before death.

Cases of recent myocardial infarction have been reported⁹ with delayed changes in the electrocardiogram. In most of these instances, if not in all, characteristic T-wave changes developed long after the clinical diagnosis was made while the S-T elevation, the early electrocardiographic sign of infarction, was missing in the first so-called "negative" records. It would appear from the evidence in our case with postmortem control, that some of these cases of myocardial infarction with delayed electrocardiographic signs may also be cases with the same peculiar location of the lesion in the myocardium leaving the subepicardial layers uninvolved.

Summary. 1. A case is reported with recent myocardial infarction, proven at autopsy, in which elevation of the S-T segment was absent in the electrocardiogram taken during the acute stage. The absence of involvement of the subepicardial myocardium over the infarcted area is considered as the possible cause for the atypical record.

2. Cases of recent myocardial infarction with delayed electrocardiographic signs also may represent such cases of infarction of the subendocardial layers without involvement of the subepicardial layers of the myocardium.

3. Other causes for absence of this electrocardiographic sign must be excluded before this interpretation is entertained.

We are grateful to Dr. D. H. Levinthal for permission to report this case. We are indebted to Dr. O. Saphir for checking the anatomic findings and to Dr. L. N. Katz for his suggestions and aid in preparing this article.

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ANEURYSM OF THE CORONARY ARTERY.

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ANEURYSMS of the coronary arteries are rare. This is clearly indicated by the fact that Packard and Wechsler⁹ in a review of the literature from 1812 to 1929 were able to find only 30 indisputable cases including one of their own. Twelve of the aneurysms were classified as arteriosclerotic, 7 as mycotic embolic, and 1 as pure mycotic in origin. Syphilitic aortitis was associated with 3 of the aneurysms of arteriosclerotic type, but it was believed not to have been an important factor in their development. In the remaining cases, the aneurysms could not be classified as to etiology.

The writer has been able to find reports of only 15 additional cases in the literature since Packard and Wechsler's survey in 1929. In 3 of these cases^{2,5,10} the aneurysm belonged to the arteriosclerotic group. Vogelsang¹³ cited a case in which aneurysm of the coronary artery was associated with gummatous myocarditis. In a remarkable case reported by Snyder and Hunter¹² a syphilitic aneurysm of the coronary artery was secondary to the burrowing of a syphilitic aneurysm of the sinus of Valsalva. Monahan⁸ has also reported a case and cited one of Seydel's believed to be of syphilitic origin. Harris⁷ collected 4 cases from the literature and added one of his own in which aneurysmal dilatation of the coronary artery was of congenital origin. Other coronary abnormalities that could perhaps be regarded as congenital aneurysms have been more properly considered in the literature under the heading of congenital anomalies of the coronary arteries. Rae¹¹ found aneurysmal dilatation of both coronary arteries in a case of rheumatic carditis. The coronary arteries were involved by an exudative, necrotizing inflammatory process suggesting that the aneurysms were also of rheumatic etiology. However, the possibility that the inflammatory reaction had been superimposed on a congenital lesion was pointed out. Abbott and Chase¹ have reported from this institution an additional case of mycotic embolic aneurysm of the coronary artery. De Navasquez³

in a study of embolic myocarditis, cited one more case in which a mycotic embolic aneurysm of a coronary artery had occurred.

Of the 45 cases of aneurysm of the coronary arteries cited above, 35 were classifiable according to etiology. Fifteen of these were arteriosclerotic; 4 were syphilitic; 5 were of congenital origin; 1 was rheumatic; 9 were mycotic embolic, and 1 was pure mycotic. The case presented here is an additional example of aneurysm of the coronary artery of the mycotic embolic variety.

Case Report. The patient, a 45-year-old white male, a physician, was admitted to the Royal Victoria Hospital, Montreal, on August 8, 1939. Twenty years previously a diagnosis of rheumatic endocarditis had been made. Since that time he had led a cautious life and had not had any serious illnesses. Four months before admission to hospital, he had experienced chills and fever which, together with other symptoms and signs, had led to a diagnosis of subacute bacterial endocarditis. After admission to hospital this diagnosis was confirmed by the additional finding of *Strep. viridans* in blood cultures. Large quantities of sulfanilamide, sulfapyridine and heparin were administered but there was no improvement. After a severe constricting pain in the chest, on Sept. 20, he failed rapidly. Nevertheless, his death on Oct. 2, 1939 was unexpected, occurring as he was being propped up on a bed pan.

Autopsy (7 hours after death). The heart was enlarged (660 gm.) due largely to hypertrophy of the left ventricle. On the mitral valve were several large polypoid vegetations which extended along the chordæ tendineæ, some of which were ruptured. The valve itself was relatively thin and showed little evidence of antecedent endocarditis. The aortic orifice, however, was markedly stenosed, its lumen reduced to a stellate opening not more than 1 cm. in greatest diameter. The aortic valve cusps were fused, thickened, nodular and extensively calcified. The appearance was typical of healed rheumatic endocarditis. Along their free edges were soft, friable vegetations which, though smaller, were similar to those on the mitral valve. In the *anterior ramus descendens of the left coronary artery*, 2 cm. from its origin there was a saccular aneurysmal dilatation measuring 1.9 cm. in length and 1.6 cm. in its greatest diameter. The aneurysm caused a prominent bulge on the external surface of the heart, but had not ruptured. Its lumen was partially filled with thrombus material. The lumen of the artery as it entered the aneurysm was patent but at the distal exit it was occluded by thrombus material. The *myocardium* of the anterior wall of the left ventricle and of the interventricular septum near the apex showed evidence of recent infarction, being softened and discolored by yellow and red mottling. Mural thrombi were found attached to the endocardial surface of the right ventricle near its apex and in the right auricular appendage, but not in the left ventricle.

The *left pulmonary artery* was found to be occluded by a large unattached embolus composed of thrombus material similar to that found on the walls of the right side of the heart. The *spleen* was soft and large, weighing 705 gm.; it contained several large irregular infarcts of recent origin. Several smaller recent infarcts were found in the *kidneys* and there were small areas of infarction in the *mesentery* and *wall of the ileum*. In addition to these findings there was generalized arteriosclerosis of moderate degree, bilateral hydrothorax and chronic passive hyperemia of the lungs, liver and kidneys.

Histology. The mitral and aortic valves showed fibrous thickening which was slight in the former but marked in the latter. The vegetations were composed of masses of platelets with some fibrin and numerous colonies of Gram-positive cocci. Although the bacteria came close to the surfaces of the

vegetations they were almost everywhere separated from the surface by a thin layer of thrombus material. There was nothing in either the gross or microscopic appearance of the vegetations to suggest that they were different from those seen in cases of subacute bacterial endocarditis not treated with heparin. The coronary aneurysm was examined in serial sections (Fig. 1). A small segment of the circumference of the arterial wall next to the myocardium was still intact and recognizable, but the segment nearest the epicardium had been almost totally destroyed and was represented only by attenuated strands of partly necrotic muscle and elastic tissue which were stretched out to form a thin, delicate wall around the external aspect of the aneurysmal sac where it bulged into the epicardial fat. The lumen of the aneurysm was lined by a thin layer of thrombus, but it was in open communication with the lumen of the proximal segment of the coronary artery. The pericardial adipose tissue in the wall of the aneurysm was edematous, infiltrated by neutrophils and contained a few proliferating fibroblasts, while the pericardial surface over the bulging aneurysm was covered by a thin layer of fibrinous exudate. Special stains to demonstrate bacteria revealed many Gram-positive cocci in the aneurysmal wall, in the thrombus lining it and in the leukocytes around it. Sections of myocardium from the soft and discolored area of infarction showed necrosis of the heart muscle which was infiltrated in patchy fashion by considerable numbers of neutrophils. At the margins of the necrotic areas, beginning fibroblastic proliferation was apparent. Histologic sections of other organs and tissues confirmed the gross pathologic diagnoses.

Case Summary. A *Strep. viridans* infection of the mitral and aortic valve cusps, previously injured by rheumatic endocarditis, was the source of infected emboli which had caused multiple infarction of the spleen, kidneys, mesentery and ileum. One such embolus, lodging in the anterior descending ramus of the left coronary artery, had caused the development of a mycotic aneurysm at this site, while occlusion of the artery had led to infarction of the myocardium at the apex of the left ventricle. Mural thrombi in the right side of the heart formed the probable source of emboli which had occluded the left pulmonary artery. Pulmonary embolism was regarded as the immediate cause of death.

Comment. All of the 9 instances of mycotic embolic aneurysm of the coronary artery cited above, as well as the one reported here, have been associated with either vegetative or ulcerative bacterial endocarditis. In 9 of the 10 cases in which the information is available, the aortic and mitral valves were involved as follows: aortic valve alone in 4 cases; aortic and mitral valves in 4 cases; mitral valve alone in 1 case. Among 8 cases in which sex was given, 5 were males and 3 were females. The ages ranged from 22 to 45 years with an average of 31. In one of the cases⁹ there were multiple aneurysms, one of the left and two of the right coronary artery. In 8 of the remaining cases there was a single aneurysm, involving the left coronary artery in 5 cases and the right coronary artery in 3. In only 2 instances was the position of an aneurysm of the left coronary artery specified; in 1 case the aneurysm was of the anterior ramus descendens and in the other of the circumflex branch. The sizes of the aneurysms ranged from 5 mm. in diameter to the

"size of a walnut." Among 8 cases in which the cause of death was indicated, it was attributed to coronary occlusion and myocardial infarction with its sequelæ in 3 cases, including the one reported here. In 2 cases sudden death was due to rupture of the aneurysm into the pericardial sac. In 2 cases death was attributed to "mitral heart failure," and in 1 case to uremia.

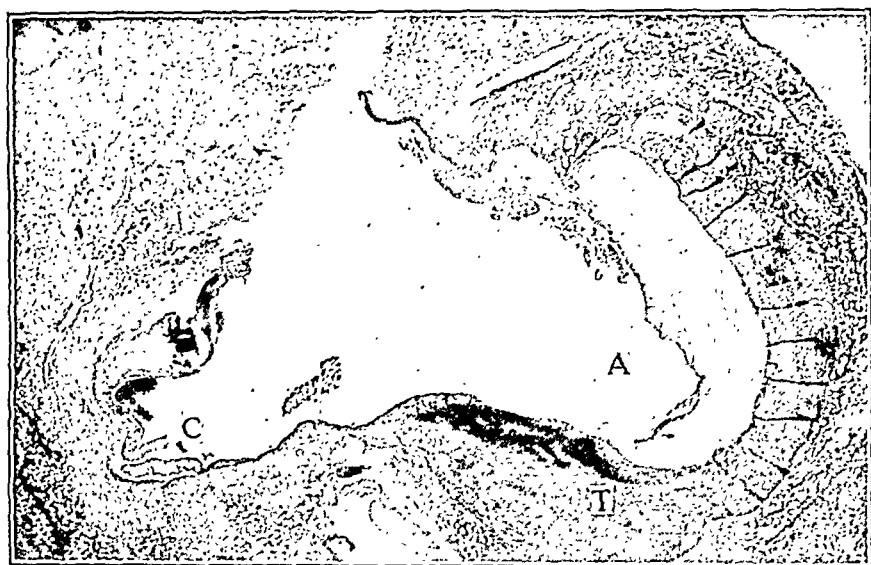


FIG. 1.—Photomicrograph (low magnification) of a transverse section of the anterior descending branch of the left coronary artery at the level of the aneurysmal dilatation. C, original lumen of the coronary artery with intact arterial wall at the left; A, lumen of aneurysmal sac; T, laminated thrombus lining the extremely thin-walled aneurysm.

The formation of mycotic embolic aneurysm of the coronary artery depends upon the lodgment of an infected embolus in the lumen of the artery. That such aneurysms are rare is due in part to the rarity of gross coronary embolism and in part to the fact that such large emboli may cause death from coronary occlusion before sufficient time has elapsed for the development of mycotic aneurysm. Although microscopic embolism of the small coronary branches is common in bacterial endocarditis, the bacteria contained in these minute emboli are rapidly phagocytized as de Navasquez has shown.³

The rarity of gross coronary embolism, has been variously attributed^{4,6} to the difference between the caliber of the aorta and that of the coronary orifices, to the situation of the coronary orifices in the sinuses of Valsalva, to the right angle of emergence of the coronary arteries, to the bulk and swiftness of the blood current in the root of the aorta and to the fact that the major part of coronary filling occurs during diastole. However, since it has been shown³ that minute emboli frequently enter the coronary arteries, it is clear

that the size of emboli large enough to occlude the main coronary branches must be the factor determining the rarity of gross coronary embolism. Emboli of sufficient size are probably not nearly as numerous in bacterial endocarditis as are minute emboli. If a great many emboli of microscopic proportions are released into the blood stream and thoroughly mixed, then it is obvious that the number of these emboli entering the coronary arteries will be in proportion to the coronary blood flow. On the other hand, larger emboli of exactly the correct size to occlude one of the coronary arteries or its main branches will much less frequently be released from the endocardial vegetations.

When an embolus of exactly the right size is released it will, by reason of its size, have greater difficulty in entering the coronary arteries, for its dimensions must be nearly as great as the diameter of the coronary orifices. The difficulty of its entrance into the coronary orifices may be illustrated by analogy with a device used by small boys in gambling with marbles. This device consists of a cigar box with a round hole cut in its lid, large enough to admit a marble freely, providing that the marble is dropped straight through the hole. However, unless the aim is accurate, the marble strikes the edge of the hole, bounces away and does not enter the box. In the same way, an embolus only a little smaller than the coronary orifices probably does not enter unless it is carried directly into the orifice without being deflected by impact with its margins.

Summary. A case of mycotic embolic aneurysm of the anterior descending branch of the left coronary artery is presented. A review of the literature reveals 45 cases of coronary aneurysm and 9 of aneurysm of mycotic embolic origin. In this instance, the source of embolism was a vegetative endocarditis of mitral and aortic valves due to the *Strep. viridans*. Impaction of the infected embolus in the coronary lumen caused not only the development of aneurysm but also coronary occlusion with infarction of the myocardium. The reasons for the rarity of mycotic embolic aneurysms of the coronary arteries are briefly discussed.

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A NOTE ON THE DEVELOPMENT OF CUTANEOUS ARTERIAL "SPIDERS" AND PALMAR ERYTHEMA IN PERSONS WITH LIVER DISEASE AND THEIR DEVELOPMENT FOLLOWING THE ADMINISTRATION OF ESTROGENS.

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IN the course of a clinical study of the acquired cutaneous arterial "spider" found in subjects with liver disease, pregnancy and nutritional deficiency disorders, during the past several years observations have been made on 359 persons with these curious stigmata. Some 250 have been followed for periods varying from several days to 5 years. Certain other vascular phenomena have been noted under similar circumstances, particularly the palmar erythema, vascularization of the skin of the nose, engorgement of the nasal mucosa, vascular dilatations in the conjunctiva and the mucous membrane of the mouth. The data accumulated are now being prepared for publication.

On the basis of these observations, and from a study of various reports which have come to my attention, the idea occurred that these vascular alterations might be related to an abnormality in the metabolism of certain 17-ketosteroid hormones, particularly the estrogenic substances. It is generally agreed that estrogens are inactivated, changed or destroyed in the liver as has been shown in heart-lung-liver preparations by Israel, Meranze and Johnson.¹ Furthermore, alterations in 17-ketosteroid metabolism have been reported in persons with cirrhosis of the liver by Edmondson, Glass and Soll,² who found abnormal estrogen and androgen excretion in several instances of gynecomastia. The well-known increase in excretion of estrogenic substances in pregnancy coincides with the period during which vascular spiders and palmar erythema tend to appear.³ The acute action of estrogens upon the minute vessels in the ear of ovariectomized rabbits has been reported by Reynolds and Foster⁴ to cause dilatation. It is not unlikely that a protracted action might affect blood-vessels throughout the body as well as those of the female genital tract which have been investigated extensively. In this connection the studies of Bartelmez and Markee on the spiral arteries in the endometrium at least suggests a morphologic similarity to the cutaneous arterial spider which we have found to be a small coiled end-artery in the subcutaneous tissue.³ A study of a serially cut vascular "spider" indicates close similarity to the

endometrial end-artery pictured in a reconstruction by Jones and Brewer.⁵ An additional suggestion presented itself when we found that during the menstrual cycle, there were visible changes in the arterial spider in the skin of certain normal women who had acquired them during pregnancy.

As collateral evidence of an important ketosteroid action in relation to function of the cutaneous circulation should be mentioned the work of Edwards, Hamilton, Duntley and Hubert⁶ who found the skin of castrate and eunuchoid men to be very pale and to contain little hemoglobin and most of that in the reduced state. When the endocrine disorder was ameliorated or corrected by androgenic therapy there was a spectacular increase in the vascularity of the skin with a preponderant rise in the oxyhemoglobin. The skin of the hands and feet became distinctly red.

It was therefore decided to administer estrogenic materials to certain persons with presumptive or diagnostic evidence of liver disease. Diethylstilbestrol and alpha-estradiol-dipropionate* were used. As controls, elderly white males with coronary artery disease were treated similarly, but showed no changes in the skin.

Three white males who had been addicted to alcohol for many years were treated.

The first, a 49-year-old man had been observed to have characteristic palmar erythema during the course of a left upper and lower lobe pneumonia (Type I pneumococcus) which in turn had complicated delirium tremens. Following sulfapyrazine therapy recovery occurred and the color of the palms returned to normal. For 2 weeks after discharge he was given 2 mg. of diethylstilbestrol by mouth every day and examined at intervals. No change occurred in the palms, the only symptoms were slight pain in the testicles and a redness of the nasal mucosa.

The second, a 55-year-old man, had been admitted to the hospital for a right upper lobe pneumonia (Type II pneumococcus) which occurred after a bout of drunkenness. He was found to have several typical vascular "spiders." He responded to sulfathiazole therapy and when afebrile was started on 2 mg. of diethylstilbestrol by mouth which was continued for 17 days. On the fifth day of this treatment he was given an intramuscular injection of 0.4 mg. of alpha-estradiol dipropionate and this was repeated daily from the eighth through the seventeenth day. On the tenth day after institution of diethylstilbestrol therapy it was noted that the size of his vascular "spiders" had increased, and that they were redder than before. Two days later several new spots appeared and 3 days after this definite radicles could be seen branching from the central red punctum. After treatment had continued for 17 days he went home. When seen 9 days later all of the "spiders" had faded, and 2 of the newly acquired ones had disappeared.

The third subject, a 44-year-old man had cirrhosis, with jaundice, ascites, a red nose with prominent vessels and several characteristic arterial "spiders," one of which pulsed palpably. Six weeks after admission, when the jaundice and ascites had disappeared, he was given 0.2 mg. of alpha-estradiol dipropionate intramuscularly on alternate day for 5 doses. After the third injection his nose became much redder and the vessels more promi-

* The latter was supplied by the Ciba Pharmaceutical Products, Inc.

ment. He was then discharged and given 2 mg. of diethylstilbestrol daily. At the end of 2 weeks it was found that he had acquired 2 new cutaneous "spiders" and those previously noted had increased in size and prominence. By the end of the fourth week his nose was livid and the vessels were very prominent. In both palms the characteristic findings of palmar erythema, most noticeable in the ulnar pad, had appeared. This finding had not been present before. In the proximal part of the right ulnar pad a typical vascular spider had developed though they are very rare in the palm. The medication was discontinued and 2 weeks later the palms were almost normal in color except for a faint red punctum which marked the site of the vascular "spider." Several of the other spiders had faded and the nose was more nearly normal in appearance. No studies were done on the urinary ketosteroid excretion. There was no clinical suggestion that the liver functions were declining during the period in which the vascular phenomena appeared.

Discussion. The events following estrogen administration to the second and third subjects suggest that the occurrence of vascular "spiders," and palmar erythema may be related to the state characterized by an imbalance or upset in metabolism of the 17-ketosteroids. Whether this be a result of estrogenic substances acting directly upon skin vessels, or is a result of a hormonal imbalance in which androgens appear in large amounts to counteract the administered estrogens, or whether the pituitary is involved remains purely speculative. It is not certain that concurrent liver function failure did not occur, or that the compounds given did not interfere with some liver function. These possibilities remain to be investigated. No doubt other interpretations will occur to those well-versed in the perplexing literature on endocrine metabolism. These preliminary studies, along with much unpublished material on aberrant endocrine and sexual manifestations in chronic liver disease suggest that a careful study of hormonal equilibrium in liver disease should be made.

The data reported in this note are brought forward in this present incomplete state because an opportunity to continue these observations in the near future now seems remote.

Conclusion. The development of cutaneous arterial "spiders" in 2 of 3 chronic alcohol addicts and palmar erythema in 1, following therapy with potent estrogens suggests that these stigmata of liver disease, pregnancy and deficiency diseases may result from abnormal metabolism of the 17-ketosteroid hormones.

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THE PROLONGED EFFECT OF AMPHETAMINE SULPHATE IN GELATIN.*

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WHEN an aqueous solution of amphetamine sulphate is introduced parenterally, its effects wear off within a few hours. On the other hand, the elimination of the amine outlasts its physiologic effect by many hours (Richter⁴ and Beyer and Skinner¹). In the present study, an attempt was made to prolong the effects of the drug by delaying its absorption. The vehicle used for this purpose was gelatin, which was selected for the following reasons: 1, its liquefied state is readily maintained; 2, it does not irritate the tissues; 3, it produces no antigen reactions as do other proteins (Wells,⁷ Hooker and Boyd,² and Kahn and McNeil³); 4, amphetamine sulphate is a stable, water-soluble substance which is freely miscible in gelatin.

Gelatin has been previously used to prolong the effects of other water-soluble drugs such as insulin and epinephrine.

Successful results with a gelatin-epinephrine mixture have been reported by Spain, Strauss and Fuchs,⁶ who used it in the treatment of allergic conditions, such as chronic bronchial asthma. These authors reported a sharp reduction in the number of doses of epinephrine required daily when this preparation was substituted for the aqueous solution.

Procedure. The effects of amphetamine sulphate in aqueous and gelatin were compared: I On the circulatory system of man; II On the gastro-intestinal tract; 1, by Roentgen-ray studies in man; 2, by their effects on the absorption of ethyl alcohol in man, (the subjects of these studies were passive schizophrenics, with the exception of one chronic alcoholic with the residuals of Korsakoff's psychosis); 3, by direct observation of the gastro-intestinal tract in guinea pigs.

* Aided by grants from the Commonwealth of Massachusetts, the Rockefeller Foundation, and the Work-Progress Administration Project No. 22386.

I. *Effect on the Blood Pressure and Pulse Rate in Man.* The subjects received intramuscular or subcutaneous injections of the amphetamine-gelatin solution in doses varying from 20 to 50 mg. The blood pressure and pulse rate were followed for several hours, in some instances as long as 120 hours. The following week the subjects received the same dose of the drug in the aqueous solution. It was found that the effects of the injections of the amphetamine-gelatin mixture did not differ significantly from those of the aqueous solution, that is, the onset and the duration of the rise in blood pressure were practically equal following the administration of both preparations, except in a few instances in which the rise in blood pressure occurred somewhat later following the administration of

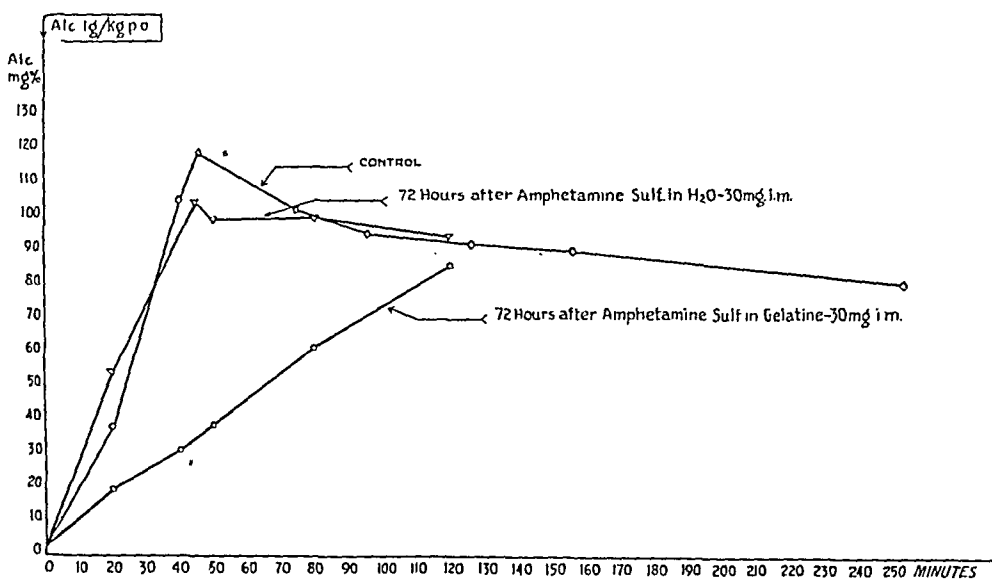


CHART 1. Prolonged effect of amphetamine sulphate in gelatin.

the amphetamine-gelatin mixture than following the aqueous solution of the drug. Equivalent decreases in the pulse rate also occurred.

II. *Effects on the Gastro-intestinal Tract.* The majority of authors agree that amphetamine sulphate in aqueous solution produces the following effects: the tonus of the stomach and intestines are decreased. This is in association with a marked dilatation and a decrease or abolition of the peristaltic movements of the stomach and colon. These changes appear to be less marked in the small intestines.

Recent investigations (Rinkel and Myerson⁵) have demonstrated another effect of amphetamine sulphate on the gastro-intestinal tract; namely, a marked delay in the absorption of ethyl alcohol.

This delay is in part due to prolonged emptying time of the stomach, and in part due to alteration of the absorptive mechanism of the small intestine which was demonstrated following direct introduction of ethyl alcohol into the duodenum.

1. *Roentgen Ray Studies in Man.* The subjects of these studies had no demonstrable disease of the gastro-intestinal tract. They were given an opaque meal (consisting of 4 ounces of barium sulphate, thoroughly stirred in 6 ounces of water), routinely used in Roentgen studies of the gastro-intestinal tract. A fasting period of 14 hours, during which no food or liquids were ingested, preceded the Roentgen ray examination. Films of the stomach with the patient lying prone, were taken at intervals of 1, 2, 3, 6 and 48 hours. In one patient, the examination was extended so that additional films were taken at 96 and 120 hours. In two instances, Roentgen rays of the colon were taken following a barium enema, 4 hours after the administration of amphetamine sulphate.

a. *Effect on the Emptying Time of the Stomach.* Both preparations delayed the emptying time of the stomach. The gelatinous mixture, however, produced a greater delay in this function than did the aqueous solution, the comparative emptying times being 3 to 6 hours and 2 to 3 hours respectively.

b. *Effect on the Tone of the Colon.* Both the aqueous and the gelatinous preparations of amphetamine sulphate produced atonicity of the colon which was characterized by shallow contractions and a decrease in number or practically complete absence of haustrations. In 2 cases, however, a marked contrast in the effects of the two preparations was apparent. In the first case, following the administration of the amphetamine-gelatin mixture, marked atonicity of the colon developed which was present even after 120 hours had elapsed. Following the administration of the aqueous solution in this subject, only slight atonicity, which lasted for 72 hours, was apparent. In the second case, in which a spastic colon did not respond to the administration of an aqueous solution of amphetamine, relaxation and atonicity were produced by administration of the gelatinous solution. These changes lasted for at least 48 hours.

2. *Absorption of Ethyl Alcohol.* In these experiments, the aqueous and gelatinous preparations of the drug were administered to fasting subjects who were then given by mouth 1 gm. of ethyl alcohol per kilo body weight. The blood alcohol level was determined at intervals up to 250 minutes after the ingestion of the alcohol. The diagram illustrates the curve of alcohol absorption in a subject at the 72-hour interval. The chart demonstrates: 1, normal alcohol absorption as a control; 2, the great inhibition of alcohol uptake 72 hours after the intramuscular injection of 30 mg. of amphetamine-gelatin mixture; 3, the return to normal of the alcohol uptake 72 hours following the intramuscular injection of aqueous amphetamine sulphate.

3. *Direct Observation of the Gastro-intestinal Tract in Animals.* Twenty-eight guinea pigs were used in these experiments. Direct exposure of the gastro-intestinal tract was carried out under local anesthesia. These animals are very responsive to amphetamine sulphate and yet tolerate the drug in doses as high as 10 mg. per kilo body weight. If the dosage is further increased, the animals die after developing convulsions. The animals were divided into 4 groups:

1. Control (6 animals),
2. Receiving intramuscular injections of amphetamine sulphate in aqueous solution (4 animals).

3. Receiving intramuscular injections of the amphetamine-gelatin mixture (14 animals). Of this group, 3 animals were examined in 24 hours; 6 in 48 hours; 4 in 72 hours, and 1 in 120 hours.

3. Given epinephrine in gelatin (4 animals). One is impressed, on exposing the abdominal cavity of the animals that received the amphetamine-gelatin mixture, by the "calmness" of the gastro-intestinal tract. Only occasionally is a peristaltic wave of the small intestine observed. The stomach and colon are markedly distended, relaxed and practically without tone. The small intestine shares these latter changes, but to a lesser degree. The color of the whole tract is grayish-white as though the blood were greatly diminished in quantity. In most cases, the gall-bladder is also greatly distended. The duration of these effects is at least 72 hours following a single injection of amphetamine-gelatin mixture, and it is only after an interval of 120 hours that the gastro-intestinal tract is restored to its normal state. Although similar changes were noted in the animals who received the aqueous preparation of amphetamine sulphate, they lasted for only 1 to 2 hours. In the control group, none of the above changes were noted. In the animals that received epinephrine in gelatin, none of the changes observed following the administration of amphetamine were noted 24 hours after administration of the drug.

Summary. The following comparative effects of amphetamine-gelatin mixture and aqueous amphetamine solution were observed:

1. **Circulatory System:** The increase in blood pressure and the corresponding decrease in pulse rate produced by amphetamine was not delayed or prolonged when the drug was dissolved in gelatin.

2. **Gastro-intestinal System:** There was a definite prolongation of the characteristic effects of amphetamine sulphate (decrease in tone and peristalsis) when the drug was mixed with gelatin. This action was observed in man following Roentgen ray studies, and in animals by direct observation of the gastro-intestinal tract.

3. The delay in absorption of alcohol which follows the administration of amphetamine sulphate is definitely more marked when the drug is mixed with gelatin.

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THE TREATMENT OF UNDERWEIGHT WITH INSULIN.

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SINCE Pitfield¹³ observed a gain in the weight of children by the use of insulin, and the report of Falta⁶ confirming in adults Pitfield's experiments, many clinical and experimental papers have appeared in the literature dealing with the use of insulin in non-diabetic malnourished patients and the mechanism by which this hormone acts.^{1-3,7,9-11,15}

Though there are many contradictory opinions regarding the mechanism of action of insulin in bringing about a gain in weight, it seems that the more accepted explanation is that insulin, by vagal action,^{14,16} produces hypermotility of stomach and hunger sensation, this action being enhanced by the hypoglycemia which results.⁵ Besides, as observed by Okada *et al.*¹² and by Lueders and Watson,⁴ insulin in sufficient amounts brings about an increase in the amount of gastric and biliary secretion, and consequently a better digestion and assimilation of the food.

Plan of Treatment. Our plan of treatment, based on physiologic and experimental grounds, is original so far as we know. Insulin is injected only once a day in order to avoid a compensatory inhibition of the internal secretion of the pancreas for lack of natural stimulus by way of alimentation. Insulin, if injected before every meal, would take care of the postprandial hyperglycemia, leaving the pancreas without action. As Clark, Gibson and Paul¹ observed, there is lowered tolerance for glucose in individuals taking insulin, evidently because of lack of stimulus to the endocrine function of the pancreas.

The dosage of insulin we employ is progressive, beginning with 8 units and increasing according to the patient's appetite on the previous day, but we never have exceeded 30 units, except in Case 12 by his own mistake.

The time of injection is about 45 minutes before the noon meal. In Brazil, where this experiment was conducted, we take 2 large meals a day—one about midday and the other about 6 P.M. We advise the patients to eat when they begin to feel hungry, because the hunger reaction of insulin does not appear exactly within 45 minutes, but is subject to variation in different patients.

When the desired effect is attained with a sufficient gain in weight, we begin to discontinue the administration of insulin, not abruptly but gradually, injecting the hormone in the inverse dosage of the beginning of treatment, that is to say, if we began by injecting 8, then 10, 14, 20 units, we discontinue by giving 20, then 14, 10, 8 units, then it is completely discontinued. In this way the stimulus to the pancreas is gradually restored, so that if this gland has been spared during the treatment it regains its function progressively. The administration of insulin* only once a day and its gradual discontinuance protects the endocrine function of the pancreas. We have had no case of glycosuria in our patients after finishing the treatment.

We think it is dangerous to inject insulin more than once a day because of the possibility of inhibition of the islets of Langerhans. In cases with diabetic history in the family it is advisable to subject the patients to a glucose tolerance test to assure the possibility of instituting treatment without inconvenient results.

Results. All cases gained weight, this gain varying from 1 to 27 pounds (average 8.7) (Table 1).

The appetite increased considerably, as well as the palatability of the food. The unanimous statement of the patients was that they ate considerably more than formerly; to quote their expression, "as never before in their life."

Most of them observed also that the treatment had a euphoric effect. It should be pointed out, however, that the esthetic satisfaction of gaining in weight may have some influence in this feeling.

All our 30 cases were healthy persons with no other complaint except underweight and lack of appetite. Their underweight was of long standing. Their age varied from 17 to 50 years; 22 were male and 8 female.

Is the Action of Insulin a Psychic One? During the prosecution of this study we had opportunity to investigate the opinion of Freyberg⁷ that the effect of the pancreatic hormone is exercised through psychic action.

We changed the contents of insulin vials to which the patients were familiarized for sterilized physiologic solution, and acted in the

* The insulin employed in all our cases was either Lilly or Schering.

same way as though it were insulin—perforated the rubber cap, simulated to ascertain the number of units and injected this placebo. All patients subjected to this experiment complained, on the following day, of lack of appetite after the injection. When we returned to real insulin their appetite again improved. We made this observation in the middle of the treatment when the patients had already experienced an improvement in appetite. The placebo was therefore tried during 4 or 5 days in the middle of the treatment without the patient's noticing that we had changed the contents of the insulin vials. We are certain that the effect was not due to suggestion, for when we gave insulin again the patient himself informed us that something had gone wrong in the previous days in which he was getting a placebo without knowing it.

TABLE 1.—GAIN IN WEIGHT OF THE INSULIN TREATMENT.

Cases.	Patients.	Sex.	Age (yrs.).	Weight before treatment (pounds).	Units (av.).	Days of treatment.	Weight after treatment.	Gain in weight.
1	F. J. B.	M	50	101	17	20	106	5
2	O. B. J.	M	34	133	20	15	139	6
3	L. C.	F	17	118	15	20	122	4
4	A. G. O.	M	31	121	21	15	128	7
5	J. B.	M	32	97	13	12	99	2
6	A. O. L.	M	29	134	23	60	154	20
7	J. B. G.	M	29	110	20	40	121	11
8	G. M.	M	34	124	24	40	133	9
9	L. B. G.	M	32	121	20	42	134	13
10	L. M. F.	F	24	93	15	20	94	1
11	C. M. M.	F	26	95	16	30	102	7
12	M. P. B.	M	32	94	34	45	121	27
13	A. G. F.	M	35	134	20	34	149	15
14	E. C.	F	30	95	15	30	102	7
15	R. N.	M	36	105	20	45	117	12
16	J. D. A.	M	38	97	15	15	100	3
17	J. L. C.	M	24	124	20	30	131	7
18	G. V.	M	27	120	20	30	132	12
19	F. F.	M	37	101	20	30	104	3
20	J. M.	M	25	98	20	30	106	8
21	M. S.	F	25	89	19	30	98	9
22	M. R.	M	38	126	18	30	132	6
23	A. J. F.	M	23	106	20	36	118	12
24	J. C. V.	M	22	128	20	35	142	14
25	A. J. G.	M	24	119	20	15	123	4
26	V. P.	M	29	130	20	30	138	8
27	J. A. L.	M	33	103	20	34	112	9
28	L. F.	F	30	94	20	31	101	7
29	L. R.	F	34	96	16	27	101	5
30	R. V.	F	20	90	20	30	100	10
Average				109.8	19.3	30	118	8.7

Summary. 1. We have briefly reviewed the literature dealing with the use of insulin in the treatment of underweight.

2. A new plan of treatment is outlined in which the patient receives insulin only once a day in progressive doses and finishes by receiving the hormone in the inverse dosage of the beginning of his treatment.

3. The possibility of inhibition of the internal secretion of the pancreas when insulin is given several times a day is discussed.
4. The opinion that the effect of insulin in underweight is psychic is also discussed and refuted.
5. All the 30 cases submitted to treatment gained weight, from 1 to 27 pounds (average 8.7).

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THE INHERITANCE OF DIABETES INSIPIDUS.*

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THERE are a number of causes of diabetes insipidus such as brain tumor, trauma, Christian's syndrome (multiple xanthomatosis), syphilis, encephalitis, other infections and idiopathy. However, heredity is not regarded ordinarily as a cause of diabetes insipidus. Nevertheless, in reviewing the literature, there are reports which show that diabetes insipidus may be inherited and transmitted through many generations of a family. Probably, the reason inheritance has not been given much attention here is that nearly all the references on this subject are in the foreign literature.

I have observed for 5 years a boy with diabetes insipidus whose mother and grandmother had the disease. It appeared of value to present their cases and to give a review of the literature.

One of the most interesting and illuminating reports on the inherited tendencies or the familial characteristics of diabetes insipidus is that given by Weil³² and his son.³³ In 1884, when Adolph Weil³²

* The term "diabetes insipidus" means a marked polyuria and polydipsia which usually ranges from at least 6 to 10 liters a day and is relieved by pituitrin. The polyuria and polydipsia are even present during the night when the patient is in bed.

was professor in Heidelberg, he studied four generations of a family of 91 members headed by a man with diabetes insipidus and found that 24 of these had the disease. Later in 1908, his son Alfred Weil³³ continued his father's studies and found that in five generations of this family there were 35 cases of diabetes insipidus among 220 members. Two-thirds of the cases were men and one-third were women. A number of these patients lived to very old age. For example, 2 daughters who had the disease their whole life were 87 and 92 years old. The inheritance of diabetes insipidus has been known as far back as 1841 when Lacombe¹⁶ reported its occurrence in 5 males and 3 females in two generations of a family. Trousseau,³⁰ too, suggested it, and later Lanceraux¹⁷ commented on the familial tendencies of the disease in several patients.

Certain accounts by authors on the number of persons affected with diabetes insipidus in various generations of individual families may be briefly presented as follows: Deebrey,⁶ 5 cases in two generations; Wachsmuth,³¹ 2 cases in one generation; Reith,²⁷ 5 cases in two generations; Gee,¹¹ 11 cases in four generations; Pain,²⁶ 7 cases in three generations; Orsi,²⁵ 6 cases in two generations; Clay,⁵ 3 cases in one generation; Lauritzen,¹⁹ 9 cases in four generations; Sasse,²⁹ 8 cases in three generations; Marinesco,²³ 3 cases in two generations; Knopfmacher,¹⁵ 5 cases in four generations; Ehrmann,⁷ 3 cases in one generation; Marañón and Bonilla,²² 2 cases in two generations; Lange,¹⁸ 4 cases in two generations.

Other extraordinary observations on this phase of the disease have been made by McIlraith²¹ who presented 3 familial cases, 2 of which were brothers. The third case was a boy whose 3 brothers, mother, maternal grandmother and an aunt were all affected. Chase³ traced diabetes insipidus through five generations of a family which appeared remarkable in that in the fourth generation as many as 10 out of 23 children had the malady. Chester and Spiegel⁴ studied the family of a woman with polyuria whose father, paternal grandmother, maternal grandmother and a maternal aunt were similarly afflicted. Curiously, 1 child of the woman's first marriage and 1 of the second marriage had diabetes insipidus. Gänsslen and Fritz¹⁰ saw a patient with an ulcer of the stomach and diabetes insipidus who gave the history that he as well as his only son had the disease since early youth and that no amount of scolding or beating by the patient's parents could make him stop drinking water. In addition, they studied the tree of a very large family by delving into the records of births, deaths and marriages for seven generations which went back to about 1700. They found that the disease was carried through the last five generations with members with the disease in each of these. Levit and Pessikova²³ found 3 cases of familial origin out of their 16 cases of diabetes insipidus. A most interesting investigation was made more recently by Eller-

man⁸ who was consulted in 1937 by a man, aged 23 years, with diabetes insipidus since childhood. The man explained that a brother, as well as his father and grandfather, also had this syndrome. Further inquiry revealed that this family had been studied by Lauritzen¹⁹ in 1893 when it was discovered that 9 of 15 members had the disease. In 1938, this family had 73 members, of whom 26 (11 females and 15 males) were found to have polyuria. His records indicated that the majority of these patients had a daily diuresis of from 12 to 16 liters while in others it was less severe, amounting from 4 to 9 liters. He believed that the mode of hereditary diabetes insipidus seemed to be one of simple dominance.

Bulloch,² Just¹³ and Hogben¹² discussed the inheritance of the disease from certain selected references in the literature without adding any of their own cases. Bulloch² presented some detailed outlines and charts of each family tree to which he referred. In addition, there have been other contributions to this study.^{1,9,24,28} I have been unable to confirm some references on the subject or to tell the number of persons affected because of the manner in which the material was presented.

Report of a Family. Son. This patient is a 25-year-old, bright, single man of Scandinavian descent whom I have observed for approximately 5 years. His history aside from his diabetes insipidus is irrelevant. The family history is important because his mother and grandmother also had this clinical entity. Details of this will be given in connection with their cases. He has never had any brothers or sisters. His father died of heart disease at the age of 48 when the patient was 6 months old. The patient has had diabetes insipidus since infancy and was a bottle-fed baby. His mother noticed that just as soon as he could walk and reach for water, he drank all he could get and was always after it. As he grew older, he imbibed as much as 3 or 4 gallons of water a day. Most of our observations have shown that his daily fluid intake and output have been about 10 to 12 liters. Pituitrin administered intramuscularly or intranasally in sufficient amounts reduced the polyuria and polydipsia to normal.

The physical examination showed a well-developed and well-nourished young man with no abnormal findings. His height was 6 feet and his weight was 193 pounds.

A number of laboratory examinations have been made. Roentgen rays of the skull were normal. The Wassermann and Hinton tests were negative. The spinal fluid was normal. The basal metabolism was -7%. The blood findings were as follows:

	Without pituitrin	With pituitrin
Hemoglobin	90%	
RBC	4,740,000	
Hematocrit { Plasma	39%	41%
	61%	59%
Calcium	12.6 mg./100 cc.	
Phosphorus	4.3 mg./100 cc.	4 mg./100 cc.
Chloride	339 mg./100 cc.	357 mg./100 cc.
Cholesterol	294 mg./100 cc.	269 mg./100 cc.
Sugar	84 mg./100 cc.	72 mg./100 cc.
NPN	32 mg./100 cc.	34 mg./100 cc.
Serum protein	7.7 gm./100 cc.	6.5 gm./100 cc.

Mother. The patient's mother is a 51-year-old widow. She consumed much water since childhood and always took a quart or more to bed with her up to 10 years ago. At 41, about the time of her menopause, her diabetes insipidus improved and now she takes daily about 5 to 6 liters of fluids. Except for the polyuria and the polydipsia she has always been quite healthy. She had no difficulty with the pregnancy or with the birth of her son, her only child. She had 1 brother who died of tuberculosis at the age of 24. Another brother died in infancy of unknown cause. She had no sisters. Her father is 75 years old and quite well.

Her general physical examination has been normal. Her height is 65½ inches and her weight 135 pounds.

Grandmother. The grandmother was a woman who drank more than 2 gallons of water a day when she was a girl. She, too, took a quart or more of it to bed with her until the age of 60. However, she improved at the age of 40, about the time of her menopause, but she still had polyuria and polydipsia at 64, when she died of chronic myocarditis and coronary disease. She had 4 brothers, 1 of whom died of diabetes mellitus. Her height was 63 inches and her weight was 165 pounds.

Comments. Study of the records of 70 patients in this clinic with diabetes insipidus due to various causes revealed only the case presented here with a story of familial diabetes insipidus, although the familial incidence of diabetes mellitus was comparatively common in these cases and in those presented in the literature.

Diabetes insipidus is a disease which may be inherited and transmitted through many generations of a family through the maternal or paternal side to either male or female children. When this disease is inherited, it may be found rather frequently in such a family. Inherited diabetes insipidus occurs ordinarily more often in males than females and sometimes skips a generation only to appear in the next. The birth of children with the disease to normal mothers, 1 of whose parents had diabetes insipidus, suggested to some authors that the transmission of polyuria at times simulated that of hemophilia.

Inherited diabetes insipidus may appear shortly after birth or later in life. For example, Klaften¹⁴ reported a 24-year-old woman with diabetes insipidus for 21 years who gave birth to an apparently normal baby that at the age of 4 weeks already took more fluids than normal. On the other hand, the 2 brothers and sister of the family presented by Clay⁵ all developed the disease at the age of 9 years. Polyuria is never present at birth.⁴ Beginning with the age of about 2 years, the symptoms of hereditary diabetes insipidus are likely to appear.

There is a rather general impression that familial diabetes insipidus is due to a dominant gene. This view was based chiefly on the large family presented by Weil. Levit and Pessikova²⁰ believe there is questionable validity in drawing conclusions from select rather than comprehensive material gathered from the literature, as done

by Bulloch, because it creates the impression that practically every case of polyuria is a familial one. They concluded that the development of familial diabetes insipidus is due to a conditionally dominant gene showing poor penetrance. However, I believe that once diabetes insipidus has been shown to be inherited by a person, there is a good possibility that this individual may pass the disease on to some of his offspring.

Summary. This paper gives a review of the literature on familial diabetes insipidus and presents the cases of a boy, his mother and maternal grandmother, all of whom had diabetes insipidus.

Diabetes insipidus is a disease which may be inherited and transmitted through many generations of a family through the maternal or paternal side to either male or female children.

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INTRAMUSCULAR PRESSURE.

I. DURING POSTOPERATIVE DEPRESSION.*

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It has been shown¹ that variations in intramuscular pressure occur in the period of postoperative depression, and in shock. Our observations confirm these changes in intramuscular pressure following surgical procedures.

Alterations in intramuscular pressure, or "muscle tonus" as Yandell Henderson prefers to term the phenomenon, may play an important rôle in shock and allied conditions.³ The purpose of this study is to determine the nature of the intramuscular pressure changes during the natural course of the postoperative period in patients who recover without the appearance of complications after surgery.

Henderson devised an instrument, modified by Kerr and Scott,⁵ with which intramuscular pressure could be directly measured. Experimental evidence indicates that Henderson's method for the measurement of intramuscular pressure is accurate.² The accumulated data of Henderson and his co-workers show values for the muscle at rest in normal individuals of from 60 to 90 mm. of water.⁴ The pressure, in relaxed muscles, remains relatively constant from day to day.² We have found variations of from 5 to 10 mm. in the reading of the instrument, and variations on different days on the same individual within the error of reading the instrument, and occasionally an extreme of 15 mm. daily difference in the normal.

Certain factors are known to alter intramuscular pressure. Anesthesia decreases the pressure. Overventilation, the inhalation of carbon dioxide gas, the administration of strychnine, and stimulation of the skin by moving currents of air, will all increase intra-

* Read before the staff of the Cedars of Lebanon Hospital, Los Angeles, Calif., May 20, 1940.

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muscular pressure in *normal individuals*.⁴ Henderson studied 7 patients after surgery and noted a fall in intramuscular pressure on isolated readings.⁴ Other than his observations, there are no data on the entire postoperative period on patients following surgical procedures. Such data are presented in this study. Studies on intramuscular pressure, and on venous pressure in postoperative depression, shock, atelectasis, and in collapse following hemorrhage will be published in another communication.

Methods. Intramuscular pressure was measured, according to the method of Henderson in the biceps muscle.*

The apparatus can be easily constructed with the tools found in the average clinical laboratory (Chart 1). The method of obtaining readings

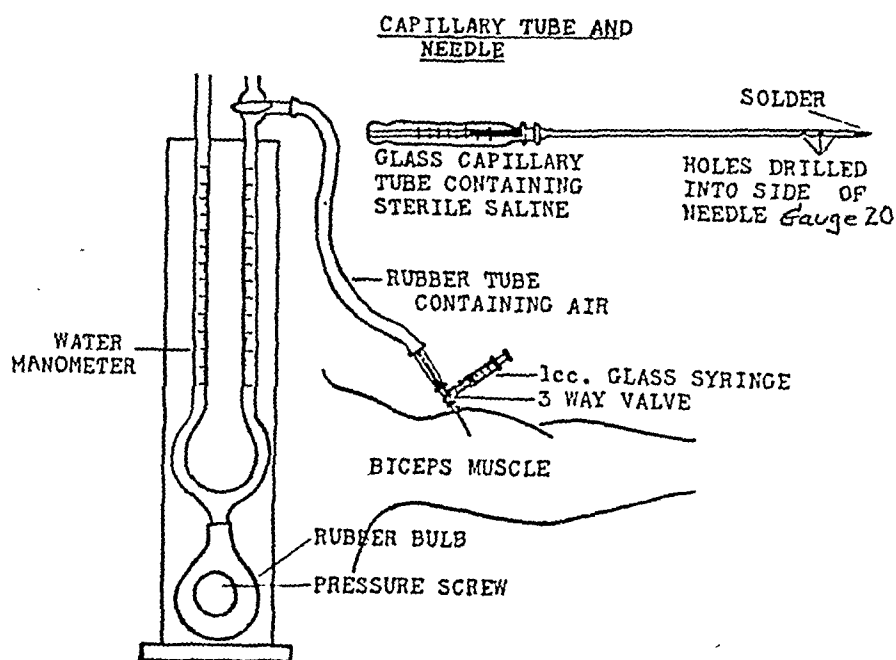


CHART 1.—The Henderson apparatus for the measurement of intramuscular pressure.

must be especially emphasized. It will be noted that the fluid in the capillary tube does not show a definite meniscus when the needle is first inserted into the muscle. As the pressure is increased by turning the thumbscrew, it will be noted that a meniscus appears with the convexity toward the muscle. The maximum curvature in the meniscus occurs when the pressure of the system is about equal to the intramuscular pressure. A slight increment of pressure within the system then starts movement of the fluid into

* The biceps muscle is easily accessible and does not have a tight fascial covering. Wells *et al.*⁶ showed that intramuscular pressure was affected by the tightness of the fascial covering of the muscle. Therefore, the biceps muscle must be used for all measurements. If another muscle is used, the normal variations for that muscle must be determined. Wells *et al.*⁶ have also published figures for intramuscular pressure on muscles of the lower extremities.

the muscle. At this point the reading is taken. The first reading is discarded and the average of the next three is recorded as the intramuscular pressure. By this technique, the maximum variations were within 5 to 10 mm. of water on subsequent readings. In this study, the pressure readings were made by the same team of two workers. One manipulated the pressure on the bulb, and the other obtained the critical point of movement of fluid in the capillary tube.

Measurements (320) of intramuscular pressure were made on 60 normals. The values varied between 60 to 90 mm. of water and corresponded with the published values of Henderson³ and of Wells *et al.*⁶

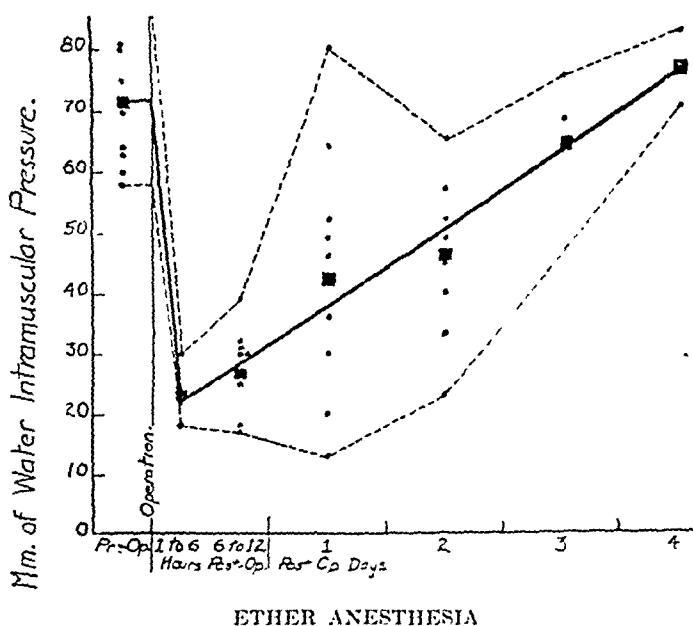


CHART 2.—The effect on intramuscular pressure of surgery under ether anesthesia in the uncomplicated uneventful postoperative course. The broken lines indicate the limits of variations in intramuscular pressure. The heavy line shows the average values. The lowest level of intramuscular pressure was noted during the first 6-hour postoperative period. A return to the preoperative level was obtained by the fourth day after operation.

The Effect of Surgery Under Ether Anesthesia. The effect of surgery under ether anesthesia was studied in 54 observations on 12 patients. Most of these were on the gynecologic service. The routine measures consisted of morphine sulphate and atropine sulphate in the preparation for anesthesia. Morphine sulphate was administered every 4 hours as needed postoperatively. Intravenous fluids chiefly of 5% glucose in saline, were administered as indicated. Carbon dioxide inhalations of the gas diluted in air were given as described by Gunther and Blond.¹ The inhalations were given at 15-minute intervals until the patient awakened; every half hour for

12 hours, and every hour during the second 12-hour period. The intervals were prolonged to from 2 to 4 hours during the next 24 to 48 hours as indicated. The inhalations were discontinued after 48 hours. No effort was made in this study to separate the effect of the various agents used in the pre- and postoperative routine. The results obtained are those of the composite picture of the routine postoperative course in this hospital. However, at a later date, these agents were studied separately on other patients. Their effect on intramuscular pressure was found to be negligible. These results will be reported in another communication.

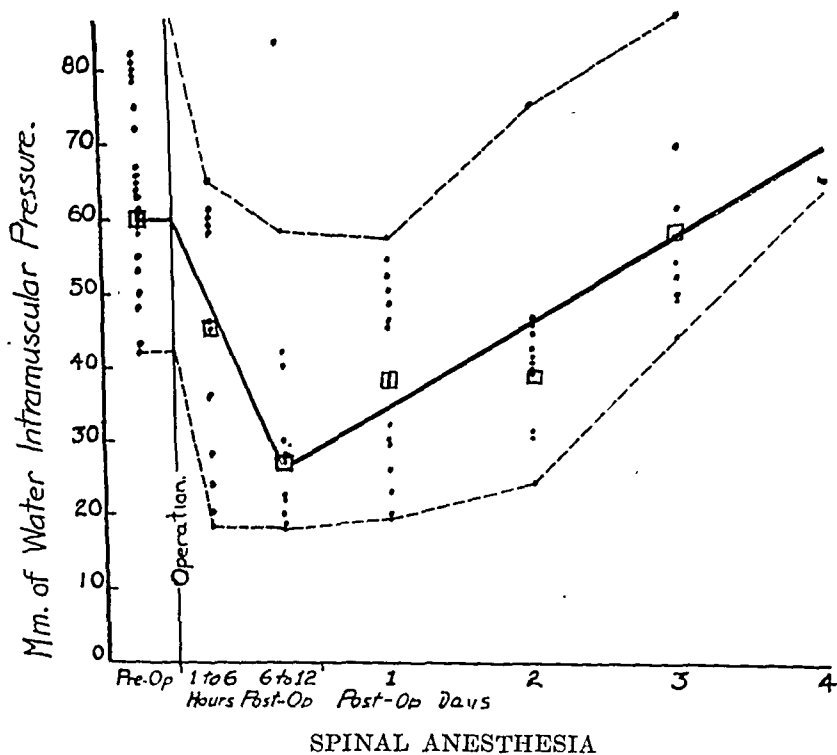


CHART 3.—The effect on intramuscular pressure of surgery under spinal anesthesia, in the uncomplicated uneventful postoperative course. The broken lines indicate the limits of variation in intramuscular pressure. The heavy line shows the average values. The lowest level of intramuscular pressure was noted during the second 6-hour postoperative period. A return to the preoperative level was obtained by the fourth day after operation.

In the patients who followed the normal, uneventful course of postoperative convalescence, a marked drop in the intramuscular pressure was observed during the first 6 hours of the postoperative period. The maximum lowering occurred at 6 hours. In the second 6-hour period, a slight rise was noted. Every patient operated upon under ether anesthesia showed a drop of intramuscular pressure to a level of from 20 to 40 mm. of water in the first 12 hours. The intramuscular pressure gradually returned to its preoperative level

during the next 4 days (Chart 1). During the excitement stage of ether anesthesia both intramuscular and venous pressures increased.

The Effect of Surgery Under Spinal Anesthesia. The effect of surgery under spinal anesthesia was studied in 130 observations on 32 patients. Most of these were from the general surgical service. The surgical procedures undergone by this group were far more formidable than in the group operated upon under ether anesthesia. The routine pre- and postoperative treatment was, however, identical (Chart 2). The anesthetic agent consisted of from 100 to 150 mg. of procain or its equivalent dosage in pantocain, or their mixtures as indicated by the need for prolonged anesthesia or a higher level of anesthesia.

The maximum drop of intramuscular pressure occurred during the second 6-hour period, in contrast to the maximum fall in the first 6-hour postoperative period in the ether anesthesia group. The extent of the drop was approximately the same. The intramuscular pressure returned to its preoperative level within 4 days postoperatively. This group also represented the uncomplicated postoperative course with an uneventful recovery.

Surgery Under Pentothal Anesthesia. Three patients operated upon under pentothal anesthesia, who had only minor surgical procedures, of short duration, showed no postoperative fall in intramuscular pressure.

Summary. A rapid drop of intramuscular pressure occurred following major surgical procedures under ether and spinal anesthesia. The intramuscular pressure reached the low level of 20 mm. of water within 6 to 12 hours after operation. In the ether anesthesia group, the lowest level was reached during the first 6-hour period after operation. The intramuscular pressure gradually returned to its preoperative level by the fourth day. These groups represent patients with uneventful postoperative courses. Pulmonary atelectasis and other complications were not present. The return of the intramuscular pressure to normal levels paralleled the clinical improvement. Surgery of a minor nature, in 3 patients under pentothal anesthesia, was not followed by a drop of intramuscular pressure.

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INTRAMUSCULAR PRESSURE.

II. THE VENOPRESSOR MECHANISM IN SHOCK-LIKE CONDITIONS
AND THE EFFECTS OF VARIOUS DRUGS.*

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In the foregoing article⁶ we showed a fall in intramuscular pressure after major surgical procedures with a return to the preoperative level by the fourth postoperative day. This communication deals with the variations in intramuscular and venous pressures as they occurred in the postoperative complications of pulmonary compression (atelectasis), shock, infection, and in collapse following massive hemorrhage.

A fall in venous pressure and a decreased volume of venous return are among the most striking physiologic changes in the circulatory failure of shock. Among the most constant pathologic findings are the high, flaccid diaphragms, the red, oozing, atelectatic lungs, and the empty heart.^{1,12,16} ‡

The theoretical basis for these alterations in respiratory and circulatory function have been postulated by Henderson.⁸ He believes that the lowered intramuscular pressure, or "muscle tonus"§ as he prefers to describe the phenomenon in shock, is one of the most important factors in the failure of the venopressor mechanism. The tonicity of the muscles of the body, he believes, is a factor of greater importance in the maintenance of the venous circulation than is that of the vasomotor mechanism. This relationship between "muscle tonus," *i. e.*, intramuscular pressure, venous pressure and the volume of flow in the venous system, he terms the "venopressor mechanism."

* Read before the staff of the Cedars of Lebanon Hospital, Los Angeles, Calif., May 20, 1940.

† Dr. Gunther is now in military service as Lieutenant-Commander, M.C., U.S.N.R.

‡ The theories advanced to explain the circulatory disturbances in shock,¹² such as the failure of the adrenal cortical hormone, disturbances in electrolyte balance, formation of the "H" substance, capillary damage and hemoconcentration, do not adequately explain the loss of intramuscular pressure, nor do they concern us here.

§ Johannes Müller, quoted by J. F. Fulton,⁴ first employed the word "tonus" as meaning a slight contractile tension characteristic of normal skeletal muscle when at rest, and he attributed this tension to the influence continually exerted upon the muscle by the nerve centers in the brain.

An agent which would increase the lowered intramuscular pressure to normal should also elevate venous pressure and restore venous flow. Furthermore, a restoration of the values of both of these physiologic functions, should be accompanied by clinical improvement in shock-like conditions. Such an agent should be a valuable adjunct in the treatment of shock.

In this study we wish to report our observations on the intramuscular and venous pressures, and the altogether unexpected and startling alterations in respiratory functions, venous and intramuscular pressure after the use of certain drugs.

Methods and Controls. The intramuscular pressure was measured with Henderson's *apparatus as modified by Kerr and Scott*.¹⁰ The sources of experimental error are discussed by Wells and Youmans¹⁷ as well as by us.⁶ The venous pressure was determined by the direct method. The auricular level was taken as being 5 cm. below the surface of the chest in the fourth interspace. The preoperative measures consisted of morphine and atropine sulphate in the preparation for anesthesia. Morphine sulphate was given every 4 hours as needed in the postoperative period for the control of pain. Fluids were administered intravenously as needed to combat dehydration and acetone ketosis. The fluids were chiefly 5% glucose in saline, or physiologic saline. Inhalations of carbon dioxide gas, diluted in air, were given as described by Gunther and Blond.⁵ The inhalations were given at 15-minute intervals until the patient awakened; every half-hour for 12 hours and every hour during the second 12-hour period. The interval was prolonged to from 2 to 4 hours during the next 24 to 48 hours.

The Separate Effect of the Different Drugs and Agents Used in the Pre- and Postoperative Routine. Morphine sulphate (gr. $\frac{1}{4}$) and atropine sulphate (gr. 1/150) were administered subcutaneously to 5 patients several days before elective surgery. No changes were noted beyond the usual 10 mm. error in reading the pressures, during a 4-hour period. Neither were changes obtained during and following the administration of from 1 to 2 liters of fluids, saline or 5% glucose intravenously in 44 observations, or of blood transfusions in 8 observations.

Despite the routine administration of carbon dioxide gas during the postoperative period, a marked lowering of the intramuscular pressure occurred. To study the effect of carbon dioxide inhalations in a markedly depressed level of intramuscular pressure, inhalations of the gas to the point of marked hyperpnea were given to 3 patients. The lowered level of intramuscular pressure did not change following the administration of the gas.

Postoperative Complications. The individual case reports herein represent a group of patients with postoperative complications. These were atelectasis, evisceration, shock and peritonitis. The effects of hemorrhage, blood transfusion, caffeine sodium benzoate, paredrine and of pyridine-beta-carboxylic acid diethylamide,* will be shown in the individual case reports.

* For the 25% solution of pyridine-beta-carboxylic acid diethylamide used in this study, we are indebted to the Ciba Pharmaceutical Products, Inc., who supplied this substance known under the trade name of Coramine. For the sake of brevity we will refer to the trade name of the drug.

Coramine has been used as a respiratory stimulant. It appears to act either on the respiratory center or on the afferent nerve endings in the carotid bulb. Henderson has pointed out that the nervous mechanism of respiration exerts a powerful influence

The effect of Coramine, CO₂ inhalation and the intravenous administration of glucose in the usual and uncomplicated postoperative course is shown in Table 1.

TABLE 1.—EFFECT OF SURGERY ON INTRAMUSCULAR PRESSURE AND THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF 5% GLUCOSE, OF THE INTRAMUSCULAR ADMINISTRATION OF CAFFEIN SODIUM BENZOATE, OF THE INTRAVENOUS ADMINISTRATION OF CORAMINE, OF THE SUBCUTANEOUS INJECTION OF STRYCHNINE SULPHATE AND OF THE INHALATION OF CARBON DIOXIDE GAS DILUTED IN AIR, ON A LOWERED LEVEL OF INTRAMUSCULAR PRESSURE.

Patient.						
H. P.		M. H.	M.	A. G.	H. E.	
Intramuscular pressure, mm. H ₂ O.	venous pressure, cm. H ₂ O.	Intramuscular pressure, mm. H ₂ O.	Intramuscular pressure, mm. H ₂ O.	Intramuscular pressure, mm. H ₂ O.	Intramuscular pressure, mm. H ₂ O.	
54	—	81	49	76	—	Before surgery.
29	10	57	19	—	—	1 hour after surgery.
—	—	—	—	43	—	3d day after surgery.
..	2000 cc. 5% glucose intravenously. Readings immediately after glucose and 6 hours after surgery.
25	5	—	—	—	—	
—	—	42	—	—	—	6 hours and 30 minutes after surgery.
—	—	31	28	43	—	Before administration of 7½ grs. caffein sodium benzoate given intramuscularly.
—	—	40	26	54	—	30 to 40 minutes later.
25	5	40	19	21	20	Before administration of 5 cc. Coramine intravenously.
49	6	51*	38	71	59	5 minutes after injection.
61	—	—	—	—	—	30 minutes later.
—	—	—	32	73	—	1 hour after injection.
—	—	—	28	—	26	Before administration of strychnine sulphate, gr. $\frac{1}{30}$ subcutaneously.†
—	—	—	26	—	20	1 hour after injection.
61	—	—	—	—	—	Before administration of inhalations of CO ₂ gas diluted in air.†
59	—	—	—	—	—	Immediately after hyperpnea.

* Intramuscularly.

† Additional data on normals will be shown in another communication.

on "muscle tonus." The pharmacology of Coramine has been discussed fully by Meier and Müller.¹¹

There is practically no danger of overdosage with Coramine, inasmuch as the toxicity is low. Furthermore, the drug carries a warning signal when the injection should be stopped, by the appearance of coughing. Even if the warning signal of cough is missed, a second warning appears in the form of mild muscular convulsions which are not serious to the patient. Convulsions appear long before the lethal dose is approached.¹⁵ We have administered as much as 30 cc. of Coramine in divided doses intravenously, within a 30-minute period to normal individuals. The only unpleasant reaction of the large dosage in normals consisted of a marked pressor effect with headache and sneezing. The pressor action seen on normals was not obtained in patients in shock-like conditions.

Case Reports. CASE 1. H. P., female, aged 42, had a supravaginal hysterectomy. Immediately after surgery, when the patient had been returned to her room the intramuscular pressure was obtained at the low level of 29 mm. of water. Five centimeters of Coramine were given intravenously. The characteristic respiratory stimulation consisting of deep and rapid inhalations, accompanied by flushing of the skin was immediate and prompt. The intramuscular pressure was obtained at 49 mm. of water, a rise of 20 mm.*

The administration of 2000 cc. of 5% glucose intravenously, and the inhalations of carbon dioxide gas in the usual postoperative procedure did not alter the level of the intramuscular pressure. The Coramine effect wore off in 5 hours and the intramuscular pressure again dropped to a low level. The patient made an uneventful recovery pursuing the usual uncomplicated postoperative course.⁶

On three occasions, the development of clinical atelectasis was observed after surgery, in shock states, accompanied by greatly lowered levels of intramuscular pressure.

CASE 2. J. S., a 58-year-old male had a partial gastrectomy for the removal of a carcinoma. The intramuscular pressure values fell steadily through the first 3 postoperative days. On the eighth postoperative day the viscera protruded through the wound. Three hours after the secondary wound closure, the intramuscular pressure dropped to 20 mm. of water (Chart 1). The venous pressure was found at the extremely low level of 1 cm. of water. The patient was stuporous and dyspneic. The pulse was rapid and thready. The face was pale and pinched and sweating was profuse. The vital signs were: pulse 160 and respirations 62 per minute, temperature 104° F., and blood pressure 140/80. The clinical picture was that of peripheral failure, or shock with vasomotor compensation maintained (compensated forward failure; Harrison⁷).

Percussion of the chest showed relative liver dullness on the right at the third rib anteriorly and flatness below the third interspace, with a corresponding level on the left. The breath sounds were suppressed and fine crepitant râles were audible at both lung bases. These physical findings were compatible with those of postoperative pulmonary atelectasis (more strictly pulmonary compression), and are frequently misdiagnosed as postoperative pneumonia.

Two doses of Coramine of 4.5 cc. each were given without results.† Following the administration of a subsequent dose of 10 cc. Coramine, the patient awakened from his stupor, became restless and 15 minutes later, when taken, there was noted a rise in the intramuscular pressure to 53 mm. of water. The rise in the venous pressure paralleled the rise of intramuscular pressure and was obtained at 12 cm. of water. Within the next 30 minutes

* Measurement of intramuscular pressure, after intravenous administration of a drug, especially in the instances where Coramine was given, was made as rapidly thereafter as technically possible. Readings of intramuscular pressure were obtained within 2 to 3 minutes, and in no instance did it take longer than 5 minutes from the time of administration of the drug.

† This was our first experience of a failure to obtain the immediate respiratory response following the intravenous administration of Coramine, in doses of 4.5 cc. Later when we studied normal individuals we found that the immediate respiratory stimulation was occasionally not obtained with the smaller dose of 4.5 cc. However, it was followed by the administration of the larger dose of 10 cc. the characteristic prompt hyperpnea ensued. As will be shown in another communication the spectacular increase of low intramuscular and venous pressures was not obtained when their values were within normal levels at the outset.

the physical signs in the chest changed. The percussion note of relative liver dullness was obtained at the fifth interspace and the breath sounds became audible, of a harsh bronchovesicular quality. The disappearance of the pulmonary compression and the descent of liver dullness, presumably the diaphragm level, was as spectacular as the changes in the intramuscular and venous pressures. During these events the blood pressure which was 135/80 remained unaltered.*

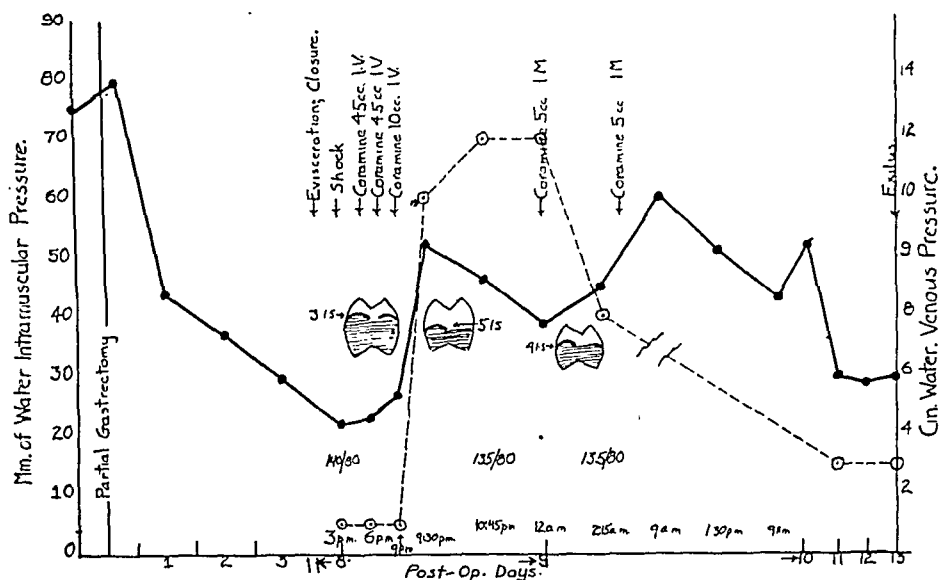


CHART 1.—Appearance of bilateral pulmonary compression (atelectasis) concomitant with the fall of the intramuscular and venous pressures in surgical shock. The administration of Coramine intravenously was followed by an immediate and marked increase in intramuscular and venous pressures. A change in the physical signs in the chest appeared within 30 minutes. The signs of pulmonary compression disappeared.

The intramuscular pressure remained at a high level during the period of two subsequent administrations of Coramine given at 3-hourly intervals by the intramuscular route. The following morning, the general condition of the patient was decidedly improved. The pulse was 120 and the respirations 32 per minute. The temperature was 99.6° F. The clinical picture of forward failure and of atelectasis had disappeared.

Infection of the peritoneal cavity developed, and during the next 11 days, the intramuscular pressure values slowly dropped and peripheral circulatory

* Postoperative pulmonary atelectasis may disappear with great rapidity following many different measures, or without any obvious reason. It is likely, that in our first cases we were dealing with "pulmonary compression" with an elevation of the diaphragms, as described by Müller *et al.*¹³ and Prinzmetal *et al.*,¹⁴ rather than with true atelectasis which according to the definition of Coryllos,³ requires pulmonary compression and bronchial obstruction. In our third observation of this condition, the respiratory response was accompanied by a severe coughing paroxysm, after which large quantities of purulent sputum were expectorated. In this instance, true atelectasis was probably present. However, from the clinical point of view, the picture of atelectasis with bronchial obstruction, as determined solely by physical and vital signs, cannot easily be differentiated from simple pulmonary compression and elevation of the diaphragms. Sufficient Roentgen ray observations have been made in papers,^{2,9,13} under similar circumstances, and in one of our cases to give authoritative weight to our observations by physical methods, relative to changes in position of the diaphragm.

collapse again appeared. Evisceration occurred again on the thirteenth day and he died shortly thereafter. The natural course of the illness was followed during the later period without further attempt to alter either the intramuscular or venous pressures.

CASE 3. S. B., age 33, female, gave us the opportunity to study the effects of intravenous fluids, the inhalations of carbon dioxide gas, the effect of the intramuscular administration of caffeine sodium benzoate and the intravenous administration of Coramine.

This patient had renal tuberculosis. Nephrectomy was performed under spinal anesthesia consisting of 100 mg. pantocain and 80 mg. procaine.

Despite the administration of 2000 cc. of intravenous fluids, a marked drop of intramuscular pressure was observed (Chart 2). The inhalation of

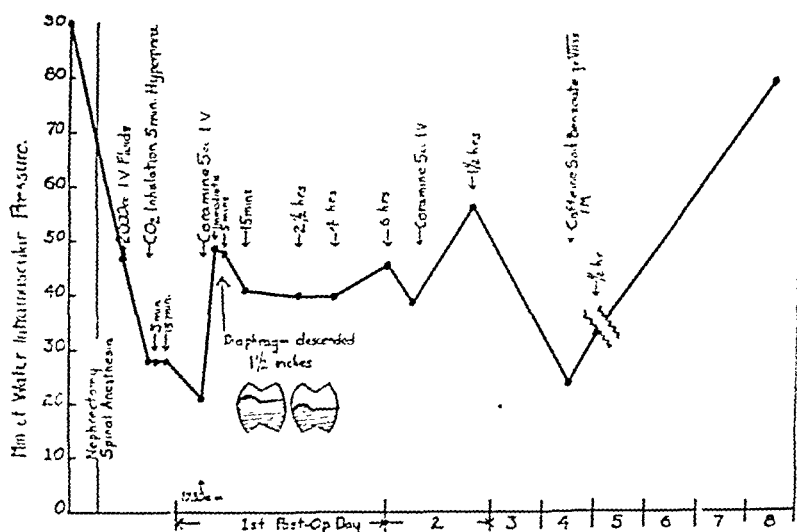


CHART 2.—A fall in intramuscular pressure, following nephrectomy, despite the intravenous administration of fluids, and of carbon dioxide inhalation to the point of hyperpnea. Concomitant with the fall of intramuscular pressure, the clinical picture of bilateral pulmonary compression (atelectasis) developed. Following the intravenous administration of Coramine, an immediate and marked increase in the intramuscular pressure occurred. The physical signs of pulmonary compression disappeared within 45 minutes. A very slight increase in intramuscular pressure followed the administration of caffeine sodium benzoate.

carbon dioxide gas for 5 minutes to the point of marked hyperpnea did not raise the level of the depressed intramuscular pressure. On two occasions, an intravenous injection of Coramine was followed by a marked rise of the intramuscular pressure. On the fourth postoperative day 7 1/2 gr. of caffeine sodium benzoate was given intramuscularly and a slight increase in the intramuscular pressure was noted one half-hour later. From this point on, the patient made an uneventful recovery.

As in the previous patient, at the time when the level of the intramuscular pressure was severely depressed, coincidentally, pulmonary complications were noted. The physical signs of pulmonary compression, and the clinical picture of bilateral pulmonary atelectasis at the bases were noted. The pulse was 120 and respirations 30 per minute. The temperature was 100.4° F.

Following the administration of Coramine, a marked rise occurred in the intramuscular pressure. Simultaneously, the level of the diaphragms, determined by percussion of liver flatness on the right, and by percussion of the lower border of lung dullness on the left, moved downward $1\frac{1}{2}$ inches. The lungs inflated, and the findings of pulmonary compression, and the clinical picture of atelectasis rapidly disappeared.

CASE 4. S. S., male, aged 54, had a cholecystectomy under inhalational anesthesia. When returned from the operating room, his intramuscular pressure was recorded at the low level of 21 mm. of water and the venous pressure at 7 cm. of water.

The blood pressure had fallen from 140 systolic and 100 diastolic to 74 systolic and 56 diastolic. The pulse was 140 and the respirations 20 per minute. The temperature was 98° F. The skin was cool, and covered with perspiration. The patient showed the clinical picture of postoperative shock with a failing vasomotor mechanism (forward failure, uncompensated).

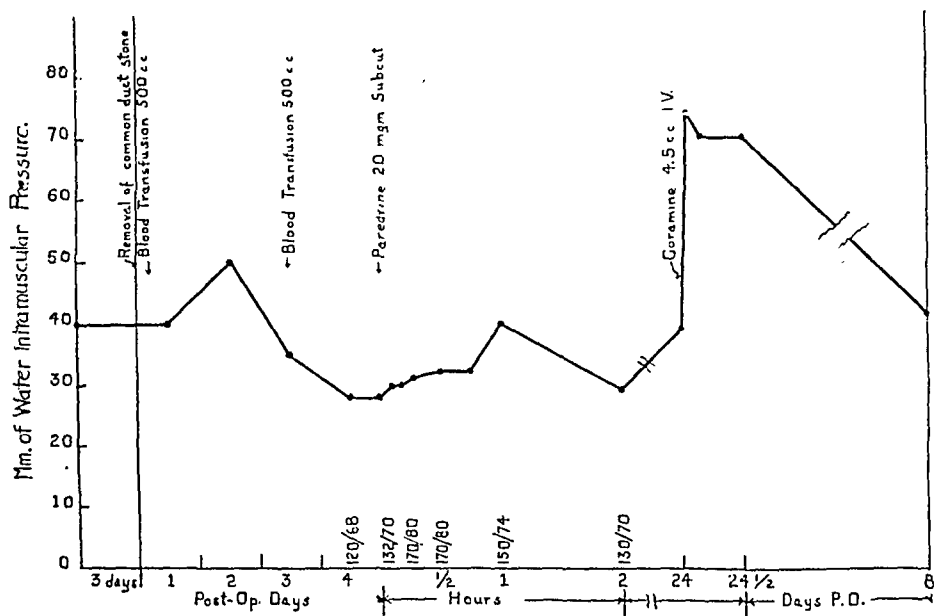


CHART 3.—The effects of blood transfusion, paredrine and of Coramine on intramuscular pressure. Despite two blood transfusions the intramuscular pressure fell to a low level. Following paredrine, the systolic blood pressure rose from 120 to 170 systolic, with no significant change in the intramuscular pressure level. Coramine given intravenously was followed by a marked and prompt increase in the intramuscular pressure.

Ten cubic centimeters of Coramine were given intravenously. Within 9 minutes the intramuscular pressure was recorded at 99 mm. of water and the venous pressure at 14 cm. of water. The skin became flushed and warm and the general appearance improved. Within 3 hours of the administration of the Coramine, the intramuscular pressure had fallen to 52 mm. of water and the venous pressure to 3.5 cm. of water.

On the fifteenth postoperative hour the intramuscular pressure was recorded at 51 mm. of water and the venous pressure at 5.5 cm. of water. The patient was again perspiring, the skin was cool, and his face pale. The pulse was 168 and the respirations 28 per minute. The temperature was 102.6° F. The blood pressure was 55 systolic and 30 diastolic, and he again showed the clinical picture of forward failure with failing compensation of the vasomotor mechanism.

The upper border of liver dullness was obtained by percussion at the 3d interspace and pulmonary dullness at a corresponding level on the left. The breath sounds were suppressed and practically inaudible at both bases. Râles were not heard. The physical signs of bilateral pulmonary compression and the clinical picture of bilateral pulmonary atelectasis were present. The elevation of the diaphragms and compression of the lungs were verified by Roentgen ray examination and were interpreted by the roentgenologist as pulmonary atelectasis.

On the sixteenth postoperative hour, 5 cc. of Coramine were given intravenously. The first readings recorded 4 minutes later showed intramuscular pressure at 99 mm. of water and venous pressure at 13 cm. of water. After 12 minutes the intramuscular pressure stabilized between 63 and 72 mm. of water and the venous pressure between 7 and 8 cm. of water. These levels were recorded during the next 20 minutes.

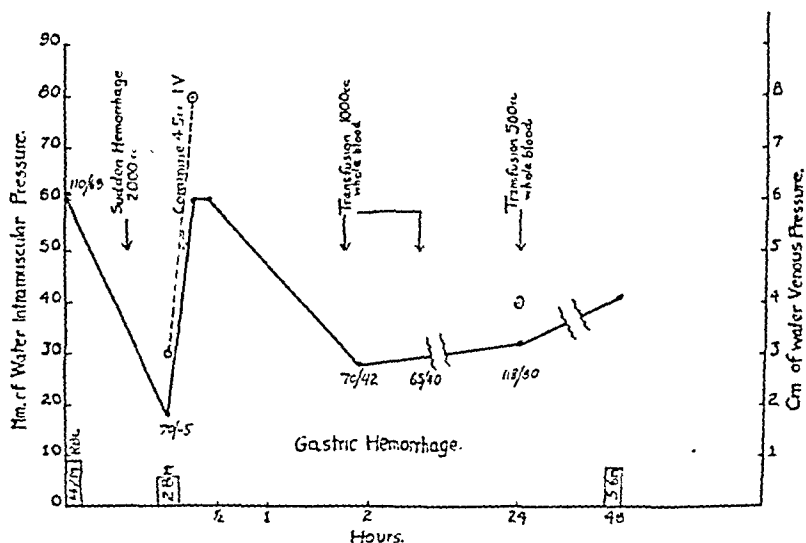


CHART 4.—The fall in intramuscular pressure, venous pressure, and of arterial pressure following a massive gastric hemorrhage associated with peripheral collapse. The administration of Coramine was followed by a prompt and marked increase in both intramuscular and venous pressures. Arterial pressure remained unchanged. Transfusion of blood did not significantly alter the levels of intramuscular pressure.

Immediately following the administration of the Coramine the patient became restless, his color changed to a flush, and he had several paroxysms of coughing, which were accompanied by the expectoration of a small "kidney basin" full of thick, tenacious greenish-yellow material.

Percussion of the lungs 22 minutes after the administration of the Coramine showed the upper border of the liver dullness at the 5th interspace with a corresponding level of pulmonary dullness on the left. Breath sounds were audible, of a harsh bronchovesicular quality, and many fine râles were audible at both bases.

The following morning, *i. e.*, 12 hours after the administration of the Coramine, the intramuscular pressure was recorded at 51 mm. of water and the venous pressure at 5.4 cm. of water. The temperature was 100° F. The pulse 130 and the respirations 30. The physical signs of incomplete aëration were still present at the bases and were verified by Roentgen ray.

but the general condition of the patient had improved and the clinical picture of forward failure was no longer present. The patient developed a pulmonary abscess in the upper right lobe which was diagnosed 19 days after surgery. The clinical picture of shock never returned.

Intramuscular Pressure During Infection. The effect of severe infection was observed in 3 patients. The intramuscular pressure fell to a low level, similarly as was seen in the patient with post-operative depression, shock, or after hemorrhage with shock.

CASE 5. H. E., female, aged 56, was operated for acute appendicitis with rupture. Diffuse peritonitis developed. The intramuscular pressure shown in Table 1, was at the low level of 36 mm. at the time of operation and dropped to 22 mm. where it remained until the second postoperative day when Coramine was administered.

CASE 6. A. G., male, aged 60, was operated for mastoid infection due to pneumococcus Type III. The preoperative intramuscular pressure was 80 mm. and 72 mm. the day of operation. Four days later with a full picture of meningitis, septicemia and heart failure, the intramuscular pressure had fallen to 21 mm. The clinical picture was that of severe toxemia

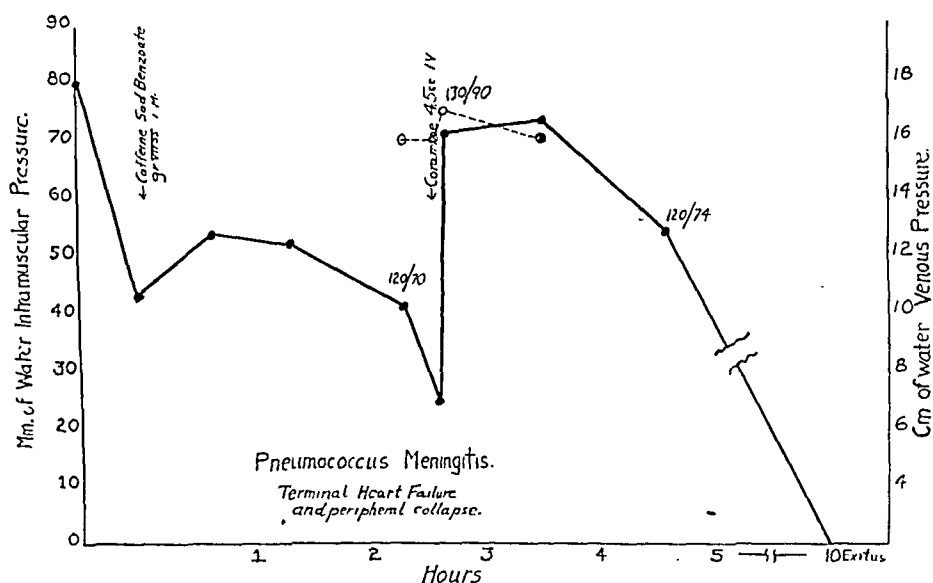


CHART 5.—The effect of caffeine sodium benzoate on a lowered intramuscular pressure, and the drop in intramuscular pressure during the depression of acute infection. The intravenous administration of Coramine was followed by a prompt and marked increase in intramuscular pressure.

and shock (Chart 5; Table 1). In J. S. (Case 2; Chart 1), as the peripheral failure appeared during the progress of peritonitis, the values for intramuscular and venous pressures both fell to low levels. However, in A. G. (Chart 5) both peripheral failure (associated with acute toxemia) and congestive heart failure are represented. The intramuscular pressure at the height of the infection was at the low level of 20 mm. of water and the venous pressure was at the high level of 16 cm. of water.*

* We have also observed the combination of normal values for venous pressure and low levels for intramuscular pressure in patients with acute coronary thrombosis, with shock, without congestive heart failure. Intramuscular pressure after coronary occlusion will be the subject of another communication.

The response of a lowered intramuscular pressure to the intravenous administration of Coramine in all three examples of the depression of infection was as prompt, spectacular and of a similar magnitude seen after its administration in the collapse of massive hemorrhage or in shock states (Charts 1, 4, 5; Table 2).*

TABLE 2.—EFFECT OF MASSIVE HEMORRHAGE ON INTRAMUSCULAR PRESSURE AND THE EFFECT OF CORAMINE AND BLOOD TRANSFUSION ON A LOWERED LEVEL OF INTRAMUSCULAR PRESSURE AFTER HEMORRHAGE.

Patient.						
A. S.			R. F.			
Intramuscular pressure, mm. H ₂ O.	Venous pressure, mm. H ₂ O.	Blood pressure,* mm. Hg.	Intramuscular pressure, mm. H ₂ O.	Blood pressure, mm. Hg.	Hgb., % Sahli.	R.B.C., million.
37	—	125/65
20	3	70/30
65	8	78/42
48	—	92/60
47	—	—
Bleeding duodenal ulcer.						
After massive hemorrhage.						
3 minutes after 4.5 cc. Coramine intravenously.						
40 minutes later and before blood transfusion.						
Immediately after 500 cc. whole blood transfusion.						
Duodenal ulcer: hemorrhage with spontaneous recovery.						
20	98.60	66	3	59	Feb. 6, 1940, 8 P.M.	after large hemorrhage.
43	—	—	—	—	Feb. 7, 1940, 1 P.M.	
47	—	64	—	—	Feb. 8, 1940.	

Intramuscular Pressure after Massive Hemorrhage, and after the Transfusion of Whole Blood.

CASE 7. The effect of hemorrhage was studied on H. R., a 57-year-old white male. While on the ward, the patient suddenly vomited 2000 cc. (measured quantity) of fluid and clotted blood. The intramuscular pressure, venous pressure and the blood pressure were all recorded at a low level following the hemorrhage (Chart 4). The patient was in profound collapse. Immediately after the intravenous administration of 5 cc. of Coramine a marked rise in intramuscular and venous pressures and improvement in the clinical condition were noted. The blood pressure remained unaltered. The increase in intramuscular and venous pressures was not maintained, and 2 hours later the intramuscular pressure was again recorded at a low level. Following a blood transfusion of 1000 cc. of whole blood, no significant increase in intramuscular pressure could be recorded.

CASE 8. A. S., aged 26, suffered a sudden hemorrhage from a bleeding duodenal ulcer. Likewise, the blood pressure, venous pressure and intramuscular pressure fell to low levels (Table 2). An intravenous injection of

* The venous pressure in Chart 5, which was already high due to the backward failure (congestive heart failure), changed slightly, a variation within the error of the method, whereas the intramuscular pressure rose markedly after the administration of Coramine.

4.5 cc. of Coramine was followed by an immediate rise in venous and intramuscular pressures. A transfusion of 500 cc. of whole blood showed no change in the value of intramuscular pressure before or after the transfusion.

CASE 9. R. F., a 41-year-old female, similarly suffered a sudden hemorrhage from a bleeding duodenal ulcer (Table 2). She likewise showed low values for intramuscular pressure following the hemorrhage.

CASE 10. E. F., a 57-year old female (Fig. 3). Following the removal of a common duct stone, the intramuscular pressure continued to fall, despite two blood transfusions of 500 cc. each. On the fourth postoperative day the intramuscular pressure was recorded at the low level of 28 mm. of water. Paredrine,* 20 mg., was given subcutaneously. No significant change in the intramuscular pressure was noted over a 2-hour period. The blood pressure, however, rose from 120 systolic to 170. In contrast, 4.5 cc. of Coramine, given intravenously the next day, was followed by a marked rise in intramuscular pressure (Table 3).

TABLE 3.—EFFECT OF PAREDRIANE AND CORAMINE ON A LOWERED LEVEL OF INTRAMUSCULAR PRESSURE.

E. F.		
Intramuscular pressure, mm. H ₂ O.	Blood pressure, mm. Hg.	
28	130/68	April 20, 1940, 3.30 P.M., 20 mg. paredrine subcutaneously.
31	132/70	5 minutes later.
29	162/74	10 minutes later.
31	170/80	15 minutes later.
33	170/80	30 minutes later.
32	165/74	45 minutes later.
41	150/74	60 minutes later.
29	130/70	2 hours later.
39	..	April 21, 3.30 P.M., before 5 cc. Coramine intravenously.
73	..	2 minutes later.
70	..	5 minutes later.
70	..	30 minutes later.
41	..	April 24.

The lack of response after transfusion of whole blood was also seen in 3 other patients whose case histories are omitted for brevity. A total of 8 observations showed no change in the values of intramuscular pressure after the transfusion of blood, whereas the administration of 4.5 cc. of Coramine by the intravenous route, was in each instance followed by a prompt increase in its level.

Intramuscular Pressure Responses to Caffein Sodium Benzoate, Strychnine, Paredrine and Ephedrine. Six patients were studied for the effect of caffein sodium benzoate (Charts 1, 2, 5; Table 1.) The intramuscular administration of $7\frac{1}{2}$ grains of this drug was followed by a definite, although slight increase in intramuscular pressure in 4 of the 6 instances.

* The Paredrine was supplied through the courtesy of Dr. M. H. Nathanson.

The increase in intramuscular pressure was about 10 mm. of water and is theoretically within the variations of error of the method. However, all changes after caffeine were in the same upward direction.

Paredrine (20 mg. subcutaneously) was given to 5 patients and ephedrine sulphate ($\frac{3}{4}$ gr.) in 1 patient during the course of spinal anesthesia. Paredrine (20 mg. subcutaneously) was given to 4 normal patients solely to study its effect on intramuscular pressure. Detailed figures are shown of a patient with low initial intramuscular pressure in Table 3 and in Chart 3.

The pressor action of Coramine which was seen in normals, was not observed by us in shock-like states wherein the intramuscular pressure was at a low level, whereas its ability to raise intramuscular pressure and venous pressure in these conditions was a constant phenomenon. In contradistinction: paredrine in addition to its pressor action, is also a venoconstrictor. It raises venous pressure for a very short time although it has no effect on a low intramuscular pressure. No attempt was made in these studies to bolster a failing vasomotor mechanism with an additional pressor substance such as paredrine. The combined action of venopressor and vasomotor drugs in shock-like states should be a physiologically sound therapeutic procedure. In no instance when given to patients under spinal anesthetic did paredrine or ephedrine prevent the fall in intramuscular pressure which has been observed following surgical procedures,⁶ nor did it alter the intramuscular pressure levels in the normals studied specifically for its effect. The administration of strychnine sulphate (gr. $\frac{1}{32}$ subcutaneously) (Table 1) likewise did not alter the intramuscular pressure.

Summary and Conclusion. Intramuscular pressure measurements were made in a variety of clinical conditions and in normal patients. In the postoperative depression following major surgery under either spinal or ether anesthesia, in the collapse following severe hemorrhage, in the depression of severe infection, and in postoperative shock, a lowered intramuscular and venous pressure was a constant observation.

Morphine, atropine, strychnine, paredrine and carbon dioxide gas, did not alter a lowered intramuscular pressure. Although paredrine constricts veins and increases venous pressure, its administration did not prevent the fall in intramuscular pressure following surgery under spinal anesthesia, nor did it raise a lowered intramuscular pressure. The intravenous infusion of fluids, glucose, saline and transfusion of blood did not alter a lowered intramuscular pressure.

Pyridine-beta-carboxylic acid diethylamide (Coramine—Ciba) was the only chemical among those tested that consistently increased the levels of intramuscular and venous pressures simultaneously. Respiration was immediately stimulated and a productive cough appeared. If in coma, the patient became semi-conscious or con-

scious. In 3 patients in severe postoperative depression, physical signs clinically indistinguishable from atelectasis disappeared with great rapidity after the administration of Coramine. This phenomenon was coincident with the restoration to normal of intramuscular and venous pressure. The clinical improvement that followed its administration in the shock-like states was most gratifying. The data presented herein support Henderson's postulates of the venopressor mechanism.

There is practically no danger of overdosage with Coramine, as the toxicity is low. Also the drug carries a warning signal, coughing and later convulsive movements long before a lethal dose is approached.

Coramine in adequate doses appears to be a valuable adjunct in the treatment of the immediate period of shock-like conditions. The improvement, of several hours' duration, affords sufficient time to enable the patient to receive the benefits of whole blood, plasma, serum, vasomotor drugs, or other useful procedures.

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BOOK REVIEWS AND NOTICES

NATIVE AFRICAN MEDICINE, With Special Reference to Its Practice in the Mano Tribe of Liberia. By GEORGE WAY HARLEY, M.D., Ganta Dispensary, Liberia. Pp. 294; Frontispiece. Cambridge, Mass.: Harvard University Press, 1941. Price. \$3.50.

EQUATORIAL and northern Africa have been brought to the fore by circumstances which are still waxing. We shall doubtless hear much about these regions, including matters medical, that is fanciful or untrue. Here we have something that is neither—it is the simple, objective story of the Mano people of northeastern Liberia and French West Africa, a story written by a medical missionary who has lived for 20 years almost exclusively among the blacks, by whom he is widely revered as a great healer. Thus, Dr. Harley has had unequalled opportunity to observe and comprehend the minds and customs of the relatively untouched natives.

Having collected the native names of 102 medicinal plants used for medical purposes, Dr. Harley was able, when back in this country on furlough, to identify many of them botanically, and also to perfect his general knowledge of African native culture. This led to an ethnologic study, over many years, especially of the secret society, the Poro Bush, which initiated the Mano youth into agricultural and political as well as magical arts.

The Mano concept of disease is here thoroughly discussed. In one of the longer chapters their rational treatment of disease is considered; but it is also shown how this logically accompanies magical treatment in the Mano mind, in some cases a mixture of the two being used. It has been especially interesting to the Reviewer to note the many similarities of customs with other primitive tribes, quite unrelated geographically, chronologically, and ethnographically (*e. g.*, the North American Indians). The medicine man, he who knows how to control mysteries, makes medicine for all human contingencies, sickness among the rest. For the sick, he uses rational remedies as readily as we do, but he must also divine and exorcise, with fetishes and ceremonies, that are just as logical to him as the purge or the splint.

This book, as a serious, well-documented study, is, to be sure, not light reading for the casual reader, nor was it meant to be. Even he, however, will find much to entertain him, a judicious selection being helped by a full index. For the anthropologist, the medical missionary, and the physician interested in primitive medicine, an intimate acquaintance with this valuable study is most warmly recommended.

E. K.

TEXTBOOK OF CLINICAL PARASITOLOGY. By DAVID L. BELDING, M.D., Professor of Bacteriology and Experimental Pathology, Boston University School of Medicine; Member of Staff of Evans Memorial, Massachusetts Memorial Hospitals. Pp. 888, 3 plates. New York: D. Appleton-Century Company, 1942. Price, \$8.50.

At the present time there are available at least two adequate and modern textbooks of Parasitology, one of them having the same title as this now under review, not to mention a "handbook" or two, or the more extensive treatises on tropical diseases. While these publications do not preclude the possibility of improvement or of competition, additional publications in this field should have more to recommend them than voluminous repetition. The present volume appears to offer little more than that. The arrange-

ment of material impresses this Reviewer as awkward, with information scattered in several subdivisions. Often, too, the author seems entirely uncritical, tending always to build up when the best evidence does not warrant it. The book does not compare with others in its field.

H. R.

DISEASES OF THE SKIN. By FRANK CROZER KNOWLES, M.D., EDWARD F. CORSON, M.D., and HENRY B. DECKER, M.D. Pp. 621; 272 illustrations. Fourth Edition. Philadelphia: Lea & Febiger, 1942. Price, \$7.00.

THE author and his collaborators, in this fourth edition, have completely revised, reorganized and modernized the text, have included additional topics, and have eliminated non-essential and out-dated material. For the most part, standard views on dermatology are expressed.

As it stands, this book is a convenient, terse, and well-illustrated text for students and practitioners. Among the especially good features are the listing of the regional distribution of common skin diseases, the various differential tables, doses in both metric and apothecary systems, and selected recent references for further consultation.

There are relatively few errata in this text. Two such are the continued use of "hereditary syphilis" (p. 414) for "congenital syphilis," which term is also used; and, on page 299 under "Xeroderma pigmentosum," Figure 95 is labeled "Xeroderma pigmentosa."

This edition further ensures the already established place of this work among the practical American texts on dermatology.

H. B.

MANUAL DE LABORATORIS DE SALUD PUBLICA. By OSCAR COSTA-MANDRY, M.D., C.T.M., Director of the Public Health Laboratories of the Department of Health of Puerto Rico; Associate Professor of Epidemiology in the School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University; Consultant in Clinical Pathology to the District Hospitals of Puerto Rico; Director of the Laboratory of the Mimiya Hospital of Santurce; and Secretary-Treasurer and Examiner in Pathological Anatomy and Bacteriology, Medical Examining Board of Puerto Rico. With a Foreword by P. MORALES OTERO, M.D., Acting Director and Associate Professor of Bacteriology and Immunology of the School of Tropical Medicine of the University of Puerto Rico. Pp. 368; 14 illustrations. San Juan: Dept. of Supplies, Printing and Transport., Govt. of Puerto Rico, 1941.

THIS laboratory manual for workers in the field of Public Health is the result of the author's experience of nearly 20 years in the manifold activities of Public Health laboratories in a tropical climate. Written not only for physicians but for lay workers, technicians and health officers, the book presents an unusual attention to details of procedure that should make it a welcome volume on every laboratory shelf in Spanish-speaking countries. The first section discusses the collection of samples; the second, the interpretation of results; the third, the procedures of technique; the fourth, the preparation of reagents and solutions, culture media, the techniques of sterilization, of filtration, of cleansing of apparatus; the care of laboratory animals; tables of weights and measures, etc. There are also appended the rules governing the functioning of the Public Health Laboratories and the laws which regulate the practice of technicians and microscopists in Puerto Rico. Well planned, written and indexed, this excellent book should find a wide appeal in all clinical laboratories, and especially in departments of public health in our sister republics to the South.

R. K.

SCIENCE AND MAN. Twenty-four Original Essays by ALES HRDLICKA, REINHOLD NIEBUHR, JACQUES MARITAIN, ALFRED E. COHN, ARTHUR H. COMPTON, HAROLD C. UREY, WALDEMAR KAEMPFERT, K. KOFFKA, BRAND BLANSHARD, JAMES T. SHOTWELL, CARL L. BECKER, JULIAN HUXLEY, BRONISLAW MALINOWSKI, FRANK KNIGHT, LEWIS MUMFORD, WALTER B. CANNON, KARL T. COMPTON, JEAN PIAGET, PHILIP C. JESSUP, HANS KELSEN, HAROLD D. LASSWELL, EDWIN G. CONKLIN, C. G. JUNG, RALPH BARTON PERRY. Edited with an introduction and conclusion by RUTH NANDA ANSHEN. Pp. 494. New York: Harcourt, Brace & Co., 1942. Price, \$4.00.

THIS book is an effort—and a successful one—to study the place of science and its achievements in the world of man, with the aim, expressed by most of the contributors, implied at least by others, of harmonizing these achievements with man's essential humanity. Twenty-four essays, representing the scientific field from anthropology to zoology, present the different aspects of "the paths we must follow if science is to become the servant rather than the master of man." These are grouped in sections on: the material, methods and ends of science, the relation of science to the universe, to society, to internationalism, and to the individual, with chapters of introduction and conclusion by the Editor, who is also the editor of the *Science and Culture Series*.

Happily the day is now passed when Science and Religion (Faith) were regarded as necessarily incompatible. With the scientist's increasing knowledge of and dominance over his surroundings, he becomes, not paradoxically, more humble as to the vastness of his ignorance and the limitations of the scientific method. It is not so difficult, then, for him to recognize that we must continue to live in the midst of the unproved and the unprovable; and that philosophy and the various sciences, all necessarily proceeding by their own special methods, must work together as best they can to preserve man as a complete microcosm properly adapted to the macrocosm of our universe. Such are some of the thoughts evoked by perusal of these essays, and what could be more important for the solution of our present problems? One naturally finds some heavy going in unfamiliar fields, but there is also much valuable description of achievement as well as rational considerations of man's relation to science that are aimed to lead the way toward returning science to the service of man.

E. K.

PSYCHOLOGICAL EFFECTS OF WAR ON CITIZEN AND SOLDIER. By R. D. GILLESPIE, M.D., Physician for Psychological Medicine, Guy's Hospital, London; Wing-Commander, Royal Air Force, Volunteer Reserve. Pp. 251. New York: W. W. Norton, 1942. Price, \$2.75.

THIS is another volume to add to the growing library on psychosomatic medicine and can be read with profit by any physician who appreciates this rapidly expanding field of medicine. Quoting the author, "The book concerns itself with general principles and the issues that are raised by the occurrence of another world cataclysm, and refers especially to psychological aspects of its causation and to the question of what can be done to prevent in some fundamental fashion its repetition. This is largely a psychological problem and the experience of war itself, as it impinges on a whole community as this one does in a way never before known, not only fills gaps in our sociological past on what happens in peacetime, but is relevant to the advice that psychologists may give for the planning of the kind of new world that is to emerge after the war." The first half of the book discusses the changing concepts, constitutional and social factors in psychoneuroses. The second portion discusses psychoneuroses among civilians and members

of the fighting forces. Both halves are replete with examples and quotations from well-known men in the field.

The opening sentences of Chapter IV are of particularly interest; they express a general trend that runs through the book: "It can be said at once that one of the most striking things about the effects of the war on the civilian population has been the relative rarity of pathological mental disturbances among the civilians exposed to air raids. Guy's Hospital, which is situated in Southwark, is in the middle of one of the most frequently bombed areas of London, and in the midst of a large population area of the poorer classes. Yet the psychiatric out-patient department which still functions there records very few cases of neuroses attributable to war conditions."

R. B.

FAMILY NUTRITION. A Monograph by Philadelphia Child Health Society. Pp. 106; 30 illustrations, 22 tables. Philadelphia, 1942. Price, free upon request.

THIS monograph covers acceptably the principles of modern nutrition and presents them in a form that will furnish to the teachers, social service workers, adult group workers, civic leaders, etc., for whom it is principally intended, information that they in turn can pass on to larger groups in schools and in the community.

It includes discussion of food requirements, the function of food, and the essentials furnished by different groups of foodstuffs. It is well illustrated and contains a number of sample menus for well-balanced meals, at various age levels.

E. W.

ENDOCRINOLOGY: Clinical Application and Treatment. By AUGUST A. WERNER, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine; Associate Physician, St. Mary's Group of Hospitals; Physician, Endocrine Clinic, Desloge Hospital and the Missouri State Hospital No. 4, Farmington, Mo. Second Edition. Pp. 924; 327 illustrations, 1 colored plate. Philadelphia, Lea & Febiger, 1942. Price, \$10.00.

THE first chapter reviews the autonomic nervous system, pointing out the importance of nervous as well as endocrine regulations in the body and noting the growing knowledge of neurohumoral relationships. This is followed by minor chapters on calorimetry, the glands in general and known and postulated hormones. In the section on the pituitary there are well-chosen tables and photographs showing osseous development from birth to maturity, age-height-weight tables, simple body measurements and body types. The author's classification of body types merges into descriptions of pituitary disorders. Here begin some of the 86 case histories, which throughout the book, serve to "highlight" the general description and enlarge its value as a diagnostic aid. Subsequent chapters present the gonads, lactation, the thyroid and parathyroid glands, the adrenals, pancreas, thymus and pineal, and so on. Short chapters on the relation of the endocrines to the skin, hair and teeth give recognition to commonly neglected minor aspects of this field. There is a short section on the diagnosis of endocrine conditions in children, in which connection the Reviewer notes with satisfaction the emphasis, in all parts of the book, on pediatric endocrinology.

The presentation of treatment is generally sound and concrete, in particular that on the care of adrenal insufficiency, and the menopausal syndrome. The author's work on involutional melancholia is well summarized.

There are occasional lapses from the general quality of this work. For example, in the preface the statement, "As a result of our present knowledge

of the functions of the ductless glands, the terms: *neurasthenia*, *hypochondria* and *nervous breakdown* are becoming obsolete" seems over-optimistic. The conclusion that testosterone relieves 50% to 70% of patients with prostatism is not supported by pathologic observation and would be unwarranted from the clinical data cited by the author on the preceding page. In the treatment of gonorrheal vaginitis in children, no mention is made of the use of sulfonamides which many prefer to estrogens. There is no mention of the recent studies on urinary ketosteroids which merit recognition in such a text, if only as the latest means of investigation.

The Reviewer concludes that there is no textbook of endocrinology comparable to the classic texts of Medicine, but that nevertheless he will frequently refer to Dr. Werner's book. It should be a distinct addition to the practitioner's library.

F. L.

THE STRUCTURE OF PROTOPLASM. A Monograph of the American Society of Plant Physiologists. Edited by WILLIAM SEIFRIZ. Pp. 283; 74 illustrations, 1 portrait. Ames, Iowa: The Iowa State College Press, 1942. Price, \$3.00.

This monograph is the printed record of a symposium on the Structure of Protoplasm presented under the auspices of the American Society of Plant Physiologists at Philadelphia on December 30, 1940, and is the first in what is planned to be a series of monographs published by this Society.

The volume deals with the modern concepts of the physical and chemical structure and properties of protoplasm, consisting of the following ten treatises: Microscopic Structure of the Cell Wall; Proteins and Protoplasmic Structure; Molecular Structure in Protoplasm; Some Mechanical Properties of Sols and Gels and Their Relation to Protoplasmic Structure; Structural Differentiation of Cytoplasm; Structural Differentiation of the Nucleus; Protoplasmic Streaming in Relation to Gel Structure in the Cytoplasm; The Relation of the Viscosity Changes of Protoplasm to Amoeboid Locomotion and Cell Division; Physical Aspects of Protoplasmic Streaming; Some Physical Properties of Protoplasm and Their Bearing on Structure.

A supplement containing communications from Kurt H. Meyer of the University of Geneva and W. T. Astbury of the University of Leeds, deals with the chemical structure of protoplasm and the importance of elongated and folded polypeptide chains in biologic structure.

The book presents a fresh modern portrayal of protoplasmic structure and behavior and should prove of value to all workers and students in biology.

D. C.

TIME AND THE PHYSICIAN. THE AUTOBIOGRAPHY OF LEWELLYS F. BARKER. Pp. 336; frontispiece, 7 illustrations. First Edition. New York: G. P. Putnam's Sons, 1942. Price, \$3.50.

Details of the life of as able and versatile a man as Dr. Barker would necessarily be of interest on their own account; they are especially so when they happen to be interwoven with an important phase of medical development in this country and with a school and hospital that, though late arrivals, played such an important part in this development. Many will naturally turn first, therefore, to the early days of the Hopkins Medical School, and to the consideration of the "full time" basis of clinical departments.

In 1902, in an address to some Hopkins alumni, Barker, then at Chicago, developed an idea that "Mall had told me" that the heads of clinical departments should be given salaries large enough to devote all their time to teaching and investigation freed from the distractions of private practice.

Unfortunately, however, when this procedure was put into effect at Hopkins in 1914, Barker, who had been head of the Department of Medicine there since 1905, was prevented by circumstances from being the first to apply the theory. In fact, like his successor, Janeway, and like Osler, he seems in his riper years to have modified considerably his views about the need for full time clinical teachers in all circumstances and localities.

In addition to the Hopkins sidelights, one reads with interest, in this entertaining work, of the author's Quaker childhood in Canada, of his Professorship of Anatomy at the University of Chicago, of the Commission to the Philippines, of plague studies in India and San Francisco, of advisory boards, committees, lectureships, memberships, honors, private practice, and the many items about which "it is given to only one man in a million to be really self-revelatory" (Jos. Collins). When one also considers how difficult it is, as Thales said, "To know one's self," the obstacles in the way of great autobiographies are obviously by no means insignificant.

E. K.

THE RAT IN LABORATORY INVESTIGATION. By JOHN Q. GRIFFITH, JR., M.D., and EDMOND J. FARRIS, PH.D. First Edition. Pp. 488; 178 illustrations. New York: J. B. Lippincott, 1942. Price, \$7.50.

THIS is a very useful book for all who are engaged in work using the rat. Thirty authors supply valuable information, derived from their own experience, as well as data compiled from the literature. Many simple, effective diagrams complement photographic illustrations.

Subjects covered include anatomy and physiology; methods of housing; diet and metabolism; technique for various physiologic methods and surgical procedures; useful tables of drug dosage; spontaneous lesions, including parasites, infections and tumors; special methods for study of the nervous system. A section on pathologic changes in the teeth under experimental conditions is particularly interesting, because it is written by those trained in dentistry, has many excellent illustrations, and includes data obtained from dental publications not often consulted by the usual investigation. Data on endocrine aspects are quite brief and scattered and not as fully illustrated as other features.

This book is a real contribution in making easily accessible much useful information for laboratory workers.

I. Z.

A SYMPOSIUM ON RESPIRATORY ENZYMES. First Edition. Pp. 281; several illustrations. Madison, Wis.: The University of Wisconsin Press, 1942. Price, \$3.00.

SOME thirty years ago when Casimir Funk coined the word "vitamin" to denote certain essential food constituents the entire knowledge of their chemical constitution could be summed up by an oversimplification in the word "amine." Today the chemistry of the vitamins roams over the entire field of organic chemistry and besides the "amines" of the B complex, such as pyridines, pyrimidines, thiazoles, alloxazines and nicotinamide, includes such diverse organic structures as ascorbic acid, polyene alcohols (A), sterols (D) and chromanes (E).

Alongside of the growth of our clinical knowledge of vitamins and their organic structure, there developed the field of the respiratory enzymes which concerned itself intimately with the chemistry of the intermediary metabolism of tissues. The discovery that essential constituents of these systems—co-enzymes—were in many instances identical with or closely related to the vitamins brought together these initially independent fields.

This fusion was fittingly celebrated in the autumn of 1941 by a combined symposium on "Respiratory Enzymes" and the "Vitamins" at the Universities of Wisconsin and Chicago. Each of 3 days' duration, they were attended by some hundred biochemists, physiologists and clinicians.

The book under review contains the papers delivered at Wisconsin which formed the chemical background for the subsequent vitamin symposium at Chicago. It illustrates how an independent rapidly growing basic science will contribute significant knowledge and help to a field of clinical medicine initially wholly unrelated.

The symposium includes discussions by the world's leading experts in the field and brings the subject of the respiratory enzymes up to the last minute in 1941. A broad interpretation of certain significant chapters is in place here. "Intermediate Carbohydrate Metabolism" (Otto Meyerhof) reviews the currently accepted views on the subject of carbohydrate breakdown in tissues. "Oxidative Mechanisms in Animal Tissues" (Eric Ball) treats in a general way the chemical means by which foodstuffs are oxidized and made to yield their energy. The subsymposium on "Hydrogen Transport" treats of the physico-chemical means by which hydrogen from the foodstuffs passes down the metabolic stream to its final combination with oxygen. The "Pasteur Effect" (Fritz Lipmann) discusses the chemistry of the aerobic and anaerobic metabolism of tissues. The discussion of "Nicotinamide" (Fritz Schlenk) shows how this important substance fits into the general scheme of metabolic co-enzymes. "Flavoproteins" (T. R. Hogness) gives the chemical background of the yellow enzymes and the related riboflavins. "Phosphorylations of Carbohydrates" (Carl Cori) again illustrates how an understanding of this fundamental mechanism is necessary for any comprehension of carbohydrate metabolism. "Metabolic Cycles" (E. A. Evans) gives the relations to tissue metabolism of the catalytic action of the 4 carbon dicarboxylic acids and of citric acid. These catalytic "cycles" have since projected themselves into discussions of cardiac embolism and aviation medicine. "Tumor Respiration" reviews the present status of this important subject. In the subsymposium on "Bacterial Respiration" is brought home again how fundamental understanding of bacterial metabolism paves the way for chemotherapy.

For the expert reader versed in chemistry and metabolism the book is unstintingly recommended. The general reader, unless he wishes to impose upon himself some weeks of arduous reading, must await the popular epitomization—still to be written—of this fascinating field. W. S.

INTERNATIONAL JOURNAL OF SEX-ECONOMY AND ORGONE-RESEARCH.

Official Organ of the International Institute for Sex-Economy and Orgone-Research. Director: WILHELM REICH, M.D. Vol. I, No. 1. Editor: THEODORE P. WOLFE, M.D. New York: Orgone Institute Press, 1942. Price, \$5 a year; single copies, \$1.25.

THE purpose of this Journal is given as the publication of material relating to the theory and practice of sex-economy and to sex-economic experimental investigation in biology and biophysics. Sex-economy is defined as a scientific theory of sexuality in its biologic, sociologic and medical aspects. This is a laudable aim for a new journal and in spite of the cryptic nature of the term "orgone-research," one naturally wishes to know more as to "how it is to be applied." It is not encouraging, especially to those not familiar with the work of the patron of this new development, Wilhelm Reich, M.D., to meet such phrases as "character-analytic vegetotherapy," "seminal stasis" (accounting, i. e., without further evidence for a plum-sized inflammatory mass in the epididymis); "pleasure is functionally

identical with a parasympatheticotonic plasma current in the direction of the periphery." One may reasonably object to the recommendation to practise masturbation in order to "achieve relaxation of the genital apparatus"; and to the recurrent emphasis on Reich's masterpiece, "Die Funktion des Orgasmus." Semantophiles, I fear, will search our dictionaries in vain for the meaning of "Orgone" (see p. 9 of Vol. I); fortunately, the special meaning to be attached to "sex-economy" has been furnished by the Editor.

Though first impressions are not favorable, one should perhaps reserve judgment on this pioneer venture, now settled in New York after having been chased about Europe by the Nazis.

E. K.

UROLOGY IN WAR. By CHARLES Y. BIDGOOD, Chief Urologist, U. S. Naval Hospital, Washington, D. C. Pp. 76; illustrations. Baltimore, Williams & Wilkins Company, 1942. Price, \$2.00.

THIS manual is described by the Surgeon-General of the Navy in a Foreword as a practical guide to officers in the field or in isolated places in dealing with urologic emergencies. He explains further that it is intended especially to aid those who are not specialists in urology. That it will fulfill these purposes in part is undoubted, but it seems to us that surgeons lacking training in urology would hesitate to apply some of the operations described.

This little book has 76 pages, the first 53 of which are largely devoted to descriptions of the pathology, symptoms and treatment of traumatic and inflammatory lesions of the genito-urinary tract. One gets the general impression that the subject matter was hastily assembled and arranged. The book is carelessly edited. The text contains much information that may be readily applied to urologic practice, but little attempt has been made to define measures applicable to various circumstances. Thus, under certain war conditions, urethral injuries may demand immediate cystotomy alone, in which event, there would be little time for study of the fascial planes of the perineum and pelvis, to detailed description of which 2 pages of the text are devoted. Nor does it seem to us that descriptions of the operative technique applicable to urethral strictures are particularly *apropos* to emergencies of urology in war. Among the few inconsistencies found is that dealing with the operative treatment of prostatic abscess; caution is at one time advised in the use of the urethral sound as a guide to drainage of such abscesses per perineum—no doubt lest the abscess be ruptured intra-urethrally—all of which is sound advice, whereas in another section, the performance of perineal prostatotomy employing urethrotomy and the use of Young's prostatic tractor, is advised for the treatment of such abscesses. The common concurrence of intra-abdominal and urinary tract injuries in war is justly emphasized. The section on traumatic injuries is as complete as could be expected, and the therapeutic measures advocated are based on sound surgical principles.

There would seem to be little justification for the page length discussion of the tabetic bladder, but the subject of bladder dysfunction after acute cerebral spinal injuries is well presented by Dr. Lloyd Lewis. Dr. Tovell's chapter on anesthesia is disproportionately long, but contains a good discussion of the various anesthetic agents and their use. There is every reason to believe that comparatively few anesthetic agents will be used in war surgery. With more careful attention paid to the relative importance of the various subjects together with their presentation in relation to their applicability under the varying circumstances encountered in war, the value of this manual would be considerably enhanced.

L. H.

SURGICAL PHYSIOLOGY. By JOSEPH NASH, M.D., Assistant Professor of Clinical Surgery, New York University College of Medicine; Associate Visiting Surgeon, Bellevue Hospital, New York City; First Lieutenant, Medical Corps, U. S. Army; Assistant Chief of the Surgical Service, Lovell General Hospital, Fort Devens, Mass. Pp. 496; 22 tables and 16 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.00.

THE importance of a comprehensive grasp of physiologic principles to the surgeon has come more and more to be recognized in the last few decades. The recent reduction in mortality and morbidity in surgical patients has been due in large part to the application of these principles in surgical practice.

Dr. Nash has chosen for this volume many of the physiologic subjects of most interest to the surgeon and has discussed certain of them in their relation to surgical problems. There is, however, a fair amount of material included that could be obtained from any textbook of general physiology and which is not, strictly speaking, surgical physiology.

Also it would seem to the Reviewer that in a book written for the general surgeon a more practical and pointed discussion of the physiologic aspects of anesthesia would be helpful.

It is to be hoped that this volume, with its many references to current literature, will find its way into the libraries of those doing general surgery.

I. R.

THE THERAPEUTICS OF INTERNAL DISEASES. Supervising Editor; GEORGE A. BLUMER, M.A., M.D.; DAVID P. SMITH, Clinical Professor of Medicine, Yale University, Consulting Physician to the New Haven Hospital; Associate Editor: ALBERT J. SULLIVAN, M.D., Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, Chief Medical Officer, Gallinger Municipal Hospital, Washington, D. C. Five Volumes, aggregating 4208 pages, with numerous illustrations. New York: The D. Appleton-Century Company, 1940, 1941. Price, \$50.00 the set.

THIS is a monumental work, representing as it does a survey of therapy in all phases of internal medicine and also in border-line zones between internal medicine and certain specialties. Space does not permit mentioning by name the 55 contributors, yet such a recital would be sufficient to convince the reader of the quality of the text, for the most of them are well known as fruitful investigators in their respective fields. To arrive at his opinions, the Reviewer has used the volumes as a source for reference daily for several months and with highly gratifying results. He is impressed both with the excellence of the editing and the conscientiousness of the Editors. In spite of the broad scope of the subject matter, there is surprisingly little duplication and there appear to be no serious omissions. Appearing early in 1940, the first volumes contained some material that was out of date when the last volume was published late in 1941. So it was that although only 4 volumes had originally been planned, a fifth was issued repeating some of the topics covered in the first and second, such as the therapeutics of the sulfonamides and of vitamins, and endocrine therapy.

Volume I begins with a section on general therapeutics, including nutrition and dietetics, medical climatology, methods and uses of the various types of physiotherapy and of radiotherapy; specific serum and vaccine therapy, non-specific shock therapy, bacteriophage therapy, endocrine therapy, occupational therapy, psychiatric treatment. The second section deals with specific therapeutic techniques, such as oral, rectal, and various methods of parenteral therapy, transfusion, spinal puncture and paracentesis. Volume II includes a section on the pharmacology and toxicology

of the more important drugs, and a section on the general care of the patient during illness and in convalescence. The major part of the volume is devoted to the treatment of infectious diseases. Volume III continues with the treatment of infections and the diseases produced by fungi, metazoa and protozoa, by poisons, by physical agents; the treatment of derangements in water and electrolyte balance; pre- and postoperative treatment; the treatment of shock. Then follow sections on the treatment of diseases of the lower respiratory tract, of diseases of the blood and lymph vessels, and of heart disease and heart failure. Volume IV contains sections on the treatment of diseases of the gastro-intestinal tract, the liver, pancreas and peritoneum; the genito-urinary tract; nephritis; diseases peculiar to women; the blood-forming organs and the locomotor system. In Volume V are considered the treatment of diseases of the nervous system and of specific psychiatric disturbances; diseases of metabolism, diseases due to allergy; the common skin diseases treatable by the general practitioner. There are also sections in chemotherapy, endocrine and vitamin therapy, bringing up-to-date the material of earlier volumes. Each volume contains an index and in addition in Volume V there is a very thorough and satisfactory general index.

The wide range of subjects covered, the excellent balance in proportion and emphasis, and above all the generally high quality of the material combine to make this work an outstanding addition to medical literature. Its advantages for all physicians as a readily available source of reference are obvious. Its chief and unavoidable disadvantage from the standpoint of the young doctor is the cost. Hospitals would both help and be helped if they were to include this set in their libraries for collateral reading by internes and junior staff members. From every angle the work is heartily recommended.

R. K.

FROM WITCHCRAFT TO CHEMOTHERAPY. The Linacre Lecture, 1941. By SIR WALTER LANGDON-BROWN, Emeritus Professor of Physic and Fellow of Corpus Christi College in the University of Cambridge. Pp. 60. Cambridge University Press. New York: The Macmillan Company, 1941. Price, \$.60.

THIS entertaining essay, after a graceful tribute to Linacre and St. John's College, Cambridge, as illustrations of the beneficent influence of tradition, proceeds to trace "the origin of witchcraft from primitive religion and the part it played in the evolution of remedies." Up through the local deities of tree and fountain to the gods of Egypt and Olympus, the "little people" and the witches of more recent times, the story leads to the nineteenth century development of modern therapeutics, in the last decade of which, for instance, "the first endocrine was given, the first antitoxin injected, while x-rays and radium were discovered." In the present century the development of the vitamins and of chemotherapy, exemplified by the arsenicals and the sulfonamides, brings the story up-to-date.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, VOL. 26, No. 3, MAY, 1942. Symposium on Gastro-intestinal Diseases. New York Number. Pp. 336; 32 illustrations. Philadelphia: W. B. Saunders Company, 1942.

THIS volume presents a good résumé of present-day concepts of the etiology, the clinical and laboratory diagnosis and the management of many gastro-intestinal disorders. The problems of peptic ulcer, simple and complicated, including detailed therapeutic measures, are thoroughly reviewed. Gastritis, gastro-intestinal allergy, chronic constipation and diarrhea, spastic colon, tuberculosis of the alimentary tract, the common digestive dis-

turbances of infants and children, primary carcinoma of the liver, traction diverticulum of the esophagus and rectocolonic lesions are ably presented from the clinician's viewpoint. The rôle of gastroscopy in modern medicine is outlined. The differential diagnosis of the acute abdomen is discussed. A short section on the office treatment of hemorrhoids and a timely presentation of the psychosomatic manifestations of gastro-intestinal disorders, together with general principles of treatment, are included. The pathologic physiology of the gall bladder and bile ducts is considered, together with some general procedures helpful in the hygiene of the biliary tract. A section dealing with the more important laboratory aids in the diagnosis of gastro-intestinal disorders brings one up to date on the clinical usefulness of these procedures.

In addition to the sections on the various digestive disorders, recent advances in certain miscellaneous fields are presented. These include discussions of the syndrome of coronary insufficiency, an interesting presentation of the clinical features of cardiac aneurysm, recent developments in digitalis therapy, especially with reference to the use of the individual cardiac glycosides, the diagnostic use of fluorescein in certain circulatory problems, and lastly, the nature, metabolism and physiology of vitamin A, together with a consideration of the diagnostic tests and the clinical manifestations of vitamin A deficiency.

J. N.

MANAGEMENT OF THE SICK INFANT AND CHILD. By **LANGLEY PORTER**, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Dean Emeritus and Professor of Medicine, University of California Medical School; and **WILLIAM E. CARTER**, M.D., Director of University of California Hospital, Out-Patient Department. Pp. 977; 95 figures. Sixth Revised Edition. St. Louis, C. V. Mosby Company, 1942. Price, \$11.50.

This reference book describes in full up-to-date detail the symptoms and therapy of the almost countless diseases and disorders which can affect the infant and child. All practitioners who deal with children will find a store of useful information here, discussing topics such as vomiting, diarrhea, nutrition, hemorrhage, prematurity, diseases of the various systems of the body, prescriptions, laboratory tests, and methods of performing scores of nursing manipulations and diagnostic maneuvers. Etiology and pathogenesis are not stressed. The index, important in a volume of this kind, is complete and adequate. The illustrations are numerous and well chosen. The fact that this book is now in its sixth edition since first published in 1922 speaks eloquently for its popularity with the profession.

L. W.

A STUDY OF THE BLOOD IN CANCER, With Special Reference to the Need of the Tumor Clinic. By **O. CAMERON GRUNER**, M.D. (LOND.). Pp. 100; fully illustrated, including graphs and colored drawings. Montreal: Renouf Publishing Company, 1942. Price, 15'.

The aim of this monograph, published under the auspices of the Archibald Cancer Fund, is to present the blood changes found in cancer cases and to show a pattern of changes which might constitute the guide to the diagnosis of cancer. Part 1 presents useful features in the morphologic examination of blood cells; Part 2, the author's method for evaluating the blood state and the effects of treatment, and a résumé of the features in the blood which he believes will assist in the diagnosis of cancer; Part 3 gives various other tests for cancer. Though the Reviewer cannot accept many of the deductions drawn (e. g., that "cancer is most certainly not present if . . . the neutrophil count is over 80%"), or even that a special pattern for cancer

blood can be demonstrated, he finds much of value in the observations presented by the author who has had great experience in these matters. We believe that this monograph demands serious study by all students of cancer.

E. K.

NEW BOOKS

History of the School of Nursing of the Presbyterian Hospital, New York, 1892-1942. By ELEANOR LEE, A.B., R.N., Assistant Professor of Nursing, Department of Nursing, College of Physicians and Surgeons, Columbia University; Instructor in History of Nursing; Chairman of the Education Committee of the Alumnae Association of the School of Nursing of the Presbyterian Hospital. Pp. 286; illustrations, over 50. New York: C. P. Putnam's Sons, 1942. Price, \$3.50.

The Modern Attack on Tuberculosis. By HENRY D. CHADWICK, M.D., Superintendent of Westfield State Sanatorium, 1909-29; Tuberculosis Controller of the City of Detroit, 1929-33; Commissioner of Public Health of the Commonwealth of Massachusetts, 1933-38; Medical Director of Middlesex Tuberculosis Sanatorium, 1938-41; and ALTON S. POPE, M.D., Chief, Bureau of Communicable Diseases, Department of Health, Chicago, 1926-29; Deputy Commissioner of Public Health and Director of the Division of Tuberculosis, Commonwealth of Massachusetts. Pp. 95; tables, 8. New York: The Commonwealth Fund, 1942. Price, \$1.00.

Clinical Cardiology. With Special Reference to Bedside Diagnosis. By WILLIAM DRESSLER, M.D., Attending Cardiologist, Israel Zion Hospital; Assistant Attending Physician, Brooklyn Hospital, New York. Pp. 692; illustrations, 108. New York: Paul B. Hoeber, Inc., 1942. Price, \$7.50.

The Prevention of Deformity in Childhood. By RICHARD BEVERLY RANEY, B.A., M.D., Associate in Orthopaedic Surgery, Duke University School of Medicine, Durham, N. C.; Attending Orthopaedic Surgeon, Watts Hospital, Durham, N. C. In collaboration with ALFRED RIVES SHANDS, JR., B.A., M.D., Medical Director, Alfred I. DuPont Institute of The Nemours Foundation, Wilmington, Del.; Visiting Professor of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa. Pp. 188; illustrated by JACK WILSON; 88 illustrations. Published and Distributed by National Society for Crippled Children in the United States of America, Elyria, Ohio, 1941. Price, \$1.00.

This little book was written as a primer for medical social workers and public health nurses who usually are the first to come in contact with crippling disease. It should also be of considerable value to the general practitioner who is without special training in orthopedics. The material is well presented in a manner that can be readily understood. The prevention of many crippling diseases is stressed in a manner that should be of interest to workers in preventive medicine. The illustrations are semi-diagrammatic and present the various crippling diseases in a clear manner.

D. A.

The Ophthalmic Formulary. Compiled by G. GRIFFIN LEWIS, M.D., F.A.C.S., Oculist to the Grouse-Irving Hospital, Syracuse. Containing the favorite prescriptions of prominent oculists from all parts of the world. Pp. 167. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.50.

This is a worthless book, unless one is interested in a compilation of favorite prescriptions by the older generation of ophthalmologists.

F. A.

NEW EDITIONS

A Textbook of Histology. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Professor of Anatomy, University of Chicago. Pp. 695; illustrations, 562, some in color. Fourth Edition. Philadelphia: W. B. Saunders Company, 1942. Price, \$7.00.

That the phrase "as dead as morphology," so frequently on the lips of the modern investigators of the cell, is unwarranted will be recognized after even a cursory inspection of this book. The advances made in histology during the past few years are epitomized in the excellent bibliographies appended to each chapter. As noted in the preface, revision was most extensive in those sections dealing with bone, nerve, spleen, and female generative system, and the eye. New figures have been added, particularly 9 photomicrographs. Perhaps in later editions the numbers of the latter may be increased at the expense of the drawings, for in the textbooks of pathology as well as in medical literature generally, photomicrographs are used almost exclusively. The student should learn, from his textbook, how to interpret the normal histologic photograph. The quality of the paper and print is excellent. H. S.

Handbook of Hygiene. By JOSEPH W. BIGGER, M.D., Sc.D., F.R.C.P.T., M.R.C.P. (Lond.), D.P.H., M.R.I.A., Professor of Bacteriology and Preventive Medicine, University of Dublin; Lieutenant-Colonel, Royal Army Medical Corps. Pp. 414; figures, 13. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

The contents of this book are subdivided into 25 chapters. The first, Vital Statistics: a brief consideration of the technique of reporting and evaluating population records, is followed by 12 chapters all of which deal with infectious diseases and the organisms involved. Then follow 5 chapters which may be grouped together as a section on "Environmental Hygiene"—Water, Food, Air and Ventilation, Disposal of Waste, and Environment being discussed. The headings of the remaining 6 chapters are Occupational Hygiene, Poisonous Gases, Maternity Infant and Child Hygiene, Personal Hygiene, The Assessment of Normal Health and the General Practitioner and the Public Health Service. The book is intended for medical students but should be equally useful to practitioners. It is well written, and adequate for its purposes. One must remember, however, that it is intended for use in Great Britain. A bit of translating would aid local understanding. H. R.

Synopsis of Materia Medica, Toxicology and Pharmacology for Students and Practitioners of Medicine. By FOREST RAMON DAVISON, B.A., M.Sc., Ph.D., M.B., Medical Department, The Upjohn Company, Kalamazoo, Mich.; Formerly Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock, Ark. Pp. 695; illustrations, 45 (4 in color). Second Edition. St. Louis: C. V. Mosby Company, 1942.

The author has revised and brought this textbook up-to-date. It is accurate, concise and can be recommended to the practising physician. It contains a good chapter on prescription writing and practical prescriptions are given throughout the text. The book contains the essential actions, uses and toxic manifestation of all useful drugs. P. D.

Aids to Physiology. By HENRY DRYERRE, Ph.D., M.R.C.S., L.R.C.P. (Lond.), F.R.S.C., Professor of Physiology, Royal (Dick) Veterinary College; Late Lecturer in Physiology, University of Edinburgh; Examiner in Physiology for Royal College of Surgeons, Edinburgh, University of Glasgow and Pharmaceutical Society of Great Britain. Pp. 396; 63 figures, several tables. Third Edition. London: Baillière, Tindall & Cox, 1942. Price, \$1.50.

This pocket sized physiology is intended as a concise epitome of the subject for use by students as an adjunct to the larger standard texts and as a "refresher" for postgraduates and others. It succeeds admirably in condensing physiology in the smallest possible space. S. G.

PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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BACTERIOLOGIC ASPECTS OF THE PREVENTION OF INFECTION.

WOUND infection would not occur if bacteria could be kept out of wounds. Therefore, for the sake of directness and clarity, it has been elected to confine this review to the bacteriologic aspects of the problem, namely, measures to keep bacteria out of wounds, and measures to remove or kill them should they succeed in entering a wound.

The means by which bacteria may enter a surgical wound are relatively few. Barring faults in technique, contaminating organisms come from the air; the skin of the surgeon, the dresser or the patient; and from surgical materials.

Air. A mass of recent work has conclusively shown that air may act as a vehicle for transmitting virulent bacteria considerable distances. The recovery of pathogenic bacteria from the air of hospital wards and operating rooms is direct evidence of this.^{1,7,18,35,64} The decreased incidence of wound infection, and of cross-infection in schools, contagious wards and surgical wards when steps are taken to lower the bacterial content of the air may be taken as indirect evidence.^{2,8,19,30,37,58,61}

The control of air-borne infection depends upon the answers to the following questions: 1, What are the sources of pathogenic bacteria found in the air of hospitals? 2, Can the aërial spread of these bacteria be prevented by controlling them at their sources? 3, If the bacteria cannot be so controlled, what can be done once they are in the air to keep them out of wounds?

Sources. Two primary sources contribute pathogenic bacteria to hospital air. These are: first, patients with respiratory infections and nasopharyngeal carriers of virulent organisms; and, second, patients suffering from infections such as carbuncle, empyema, diphtheria, and lung abscess.

Individuals expel droplets of saliva upon talking, coughing, or sneezing. By this means pathogenic bacteria escape from carriers and patients suffering from respiratory infections. In the past, emphasis has been placed upon large droplets which travel only short distances^{15,43} and were thought to spread bacteria only 6 to 10 feet. There is no doubt that these droplets are an important cause of infection when a surgeon or a dresser talks directly over an open wound.¹⁵ Meleney and Stevens³⁴ and Walker⁵² are among many workers who feel they have traced wound infections to this source.

Recently, however, Wells and his collaborators^{55,56,57,59,60} have presented evidence which has revolutionized the concepts of air-borne disease. These workers have shown that when an individual coughs or sneezes, he expels not only large droplets which because of their weight fall quickly to the ground and have only a limited direct range of infectivity, but also smaller droplets which have different characteristics.^{56,59,60} When a droplet is expelled into the air, it falls toward the ground with varying speed, depending upon its size and specific gravity, the presence or absence of air currents, the relative humidity and the speed of ejection. Many small droplets evaporate before reaching the ground and become tiny buoyant nuclei of particulate matter—the droplet nuclei. Their mass is so small in proportion to their surface area that they do not gravitate to the ground but remain suspended in the air and are wafted about for indefinite periods of time. These droplet nuclei are capable of traveling great distances. Wells and Wells⁶⁰ inoculated the humidifying water of a one-room air-conditioner in the basement of the Harvard School of Public Health with *Escherichia coli*. The building was not mechanically ventilated, but the investigators were able to recover *Escherichia coli*, presumably some of those inoculated, from the ends of every corridor up to the top floor of the three-story building where the concentration reached approximately 1% of that in the air-conditioned room. These observers have also determined the disappearance rates for 16 organisms which were introduced into the air by an atomizer.⁵⁹ Since *Staph. aureus* and *Strep. hemolyticus* are the chief offenders in surgical wound infections, it is of considerable interest to note that they survived 3 and 2 days respectively.

It is apparent, then, that both sick people and healthy nasopharyngeal carriers of pathogenic organisms discharge virulent bacteria in large droplets of saliva and in small ones which become droplet nuclei. The large droplets may fall directly into a wound or may fall upon bedding, floors, tables, and so forth, and after drying be wafted about as dust. The droplet nuclei remain in the air indefinitely and are inhaled by patients, nurses, doctors, orderlies and visitors.

The second source of bacteria which are transported through the air is infected discharges of patients such as lochia, pus from draining wounds, feces from colostomies, and ulcerating cancers. Only a naïve individual could believe that these septic materials stay confined to the inner layer of dressings. It is quite obvious to anyone who has had any hospital experience that dressings become soaked through readily, that pus and feces frequently soil the bedding and run over the patient's skin and pajamas. Willits and Hare⁶⁴ have shown that the "whole of

the contents of the bed containing a patient suffering from an infected wound" may harbor virulent organisms. Miles *et al.*³⁵ recovered *Strep. hemolyticus* from the outside of plaster casts of patients treated by the closed plaster method and from the outer surface of dressings. These organisms may be transmitted to other patients by hospital personnel, but more often by the air as particles of dust. When a bed is made or when dressings are done, these dried bits of exudate are sent flying into the air to light on other beds, dressings and open wounds. Van den Ende *et al.*⁵¹ recovered *Strep. hemolyticus* from the air of a room in which a bed was being made even though the patient was not in the room. White⁶² was able to recover *Strep. hemolyticus* from the dust of rooms which had harbored parturient patients with *Strep. hemolyticus* infections 5 days after they had left. Furthermore, a person who swept such a room 5 days after the patient had vacated it developed a streptococcal pharyngitis.

Contaminated dust is thrown into the air by sweeping, as shown by Allison and Brown¹ who found the highest incidence of *Strep. hemolyticus* in the air during the hours when sweeping and bed-making were done. Miles *et al.*³⁵ found that the bacterial content of the air of hospital wards paralleled the dust content.

Control of Sources. Can the aërial spread of these bacteria be prevented by controlling them at their sources? Those from the nasopharynx may be partially but not absolutely controlled. Hirshfeld and Laube,²³ who designed an apparatus to test the efficiency of masks in preventing the escape of both large droplets and droplet nuclei from the nose and mouth found that very few bacteria are expelled by an unmasked person breathing quietly through either the nose or mouth. During talking, however, large numbers of bacteria escape, chiefly in large droplets. Conventional masks decrease this contamination appreciably. A masked person, however, expels more bacteria into the air when he talks than an unmasked one who remains silent. There is no practical mask available which will completely prevent the escape of bacteria from the respiratory tract of an individual who is talking, coughing or sneezing. Contamination from this source, then, cannot be completely eliminated at present. It can be greatly reduced, however, by observing silence as much as possible and by wearing masks when it is necessary to talk. In the operating room, the maintenance of silence is practical. On the wards, this cannot be accomplished, but it is possible to avoid talking during dressings.

It is more difficult to prevent contamination of the air with dust-borne bacteria derived from septic discharges of patients. It was noted above that bacteria may be recovered from bedding, the outside of plaster casts, the outer layers of dressings, from patients' skin and pajamas. Any agitation of these articles sends organisms flying into the air only to alight again on other beds, on the uniforms of attendants and on the floor. Sweeping, bed-making and other necessary activities send them flying about again.

Preventing this type of spread in the operating room requires planning and a thoughtful procedure. First of all, the operating room must be built without many corners and much fixed equipment to harbor dust. Second, there should be an ample supply of sterile air. Third, the

patient must be transferred from his bed to the operating table, anesthetized, placed in position on the table, and covered with sterile covers in an anteroom. Thus his dusty, bacteria-laden bedding never enters the operating room. Fourth, the operating room staff must wear freshly laundered clothes.

Preventing the spread of dust-borne infection from wound to wound is even more difficult on the ward. Van den Ende *et al.*⁵¹ advocate oiling the floors and blankets to prevent liberation of dust when beds are made and floors are swept. Even with this precaution, the ward house-keeping should cease an hour before dressing time.⁵⁵ The linen and blankets should be changed and laundered frequently. Furthermore, dressings should be done with care. The soiled dressings must be removed with no more agitation than necessary and placed immediately in a closed container to prevent the liberation of the millions of bacteria which they contain. A rigid dressing technique, embodying these as well as many other precautions was described by McKissock, Wright and Miles.³¹ These investigators felt that strict adherence to this technique had produced a marked decrease in cross-infection.

Air Sterilization. It is obvious that it is not practical in the operating room or the wards to carry out in sufficient detail measures that will prevent absolutely the escape of bacteria from the respiratory tract or from patients' infective discharges. It has been necessary, therefore, to develop methods of killing bacteria suspended in the air, either as droplet nuclei or as dust.

The most widely publicized of these is ultraviolet light. Although the germicidal properties of ultraviolet light have been known for many years, it is only recently that this light has been employed to reduce the bacterial population of air.^{17,60} Hart¹⁹ has used ultraviolet light in his operating room at Duke University since 1935 and he is convinced that it is responsible for a marked decrease in wound infections. Overholt and Betts³⁷ also have reported on the uses of ultraviolet light. There is still, however, insufficient evidence to draw definite conclusions on the place of ultraviolet light in the operating room. While the evidence seems to be fairly conclusive that it acts by reducing the bacterial flora of the air, this is not certain. It is possible that ultraviolet light kills bacteria which have entered the wound from sources other than the air, such as the skin of the patient or the hands of the surgeon, or that it may act by making a wound more resistant to infection by virtue of the inflammatory reaction which it causes. The answers to these questions will determine whether it is necessary to radiate only the wound or whether the air of the entire room must be radiated. Furthermore, ultraviolet light is not a harmless agent. Kraissl *et al.*⁵⁴ have shown that it produces definite inflammatory reaction in the tissues and that prolonged exposure produces gangrene of guinea pigs' intestines. More work will have to be done before the place of ultraviolet light in operating rooms is established. In the case of contagious disease wards and pediatric wards, however, there appears to be evidence that it is of definite value in the prevention of cross-infection.^{8, 22, 53, 54} Here, also, final appraisal must await more evidence.

A second method of reducing the bacterial content of air is being studied, but has not yet been sufficiently developed to warrant widespread application. Trillat^{17, 54} reported that the bacterial content of

the air could be reduced by spraying germicides into it in the form of mists. These mists consist of particles approximately 0.5 micron in diameter. The particles are so small that a relatively insignificant quantity of the germicidal agent suffices to fill a room with invisible mist. The particles, furthermore, remain suspended as do droplet nuclei and barring evaporation remain in the air for considerable time. Theoretically, each small droplet contains the same concentration of the germicidal agent as the parent solution. When such a droplet meets a single bacterium, it destroys it. A number of investigators, among whom are Tworf *et al.*,⁴⁹ Pulvertaft *et al.*,^{42,43} Williamson and Gotaas⁶³ and Masterman,³² have studied aerosols in detail. While there is some disagreement among these workers, they have laid the foundation for further study and have shown that sterilization of the air in hospitals, theatres, schools, etc., with germicidal aerosols is possible and may soon be within the range of practical application. Certain facts, such as the selection of germicides, the design of apparatus for their atomization and the establishment of standards of concentration in the air remain to be established. An aerosol to be suitable for use must be non-toxic, and non-irritating to man, lethal in the concentration in which it can be used for all pathogenic bacteria which may be present in the air, non-odorous, invisible, non-corrosive, non-inflammable, and must not leave deposits or coatings on walls or furniture.⁶³

At present, aerosols are used to sterilize the air of laboratories, media, kitchens and food storage rooms. For this purpose, they are superior to ultraviolet light, for they fill all nooks and crannies while ultraviolet light travels in straight lines and cannot affect bacteria in the shadow of an object. [An important article by T. N. Harris and Joseph Stokes, Jr., on the sterilization of air in enclosed spaces by propylene glycol vapor will appear in our September number.]

Skin of the Operator. Hopeless confusion attended the efforts to determine the importance of the surgeon's hands as a source of wound contamination until Price^{39,40} devised a simple and reliable method by means of which the bacteria on the skin may be counted and the effectiveness of various antiseptics and methods of scrubbing determined. With this method, several very important facts have become evident:

(a) Complete sterilization of the skin of the hands and forearms is so difficult that practical considerations render it an impossibility.

(b) When rubber gloves are worn, conditions on the skin beneath are markedly altered, so that the generation time of the bacteria remaining after scrubbing or washing with germicides is promptly shortened to 40 to 60 minutes, and the flora rapidly increase until it may exceed by far the normal limits.

To reaffirm the latter fact, the author²² cultured gloves which had been worn for varying lengths of time. The comparative number of organisms depended upon the individual, the amount of perspiration in the glove, and the length of time it had been worn. The number recovered varied from 1000 to 1,000,000 per glove. Thus, an enormous number of bacteria may escape from a torn glove with a drop of sweat. Torn gloves emitting droplets of bacteria-laden sweat are a more dangerous cause of wound contamination than the dust and air, since ordinarily only 50 to 60 bacteria per hour fall into a wound from the air.

[The question therefore seems to be whether the partial sterility of the ungloved hand is a greater or less hazard than the chance of the torn glove.—Ed.]

Devenish and Miles⁹ have traced an epidemic of *Staph. aureus* wound infections to the flora of the hands of a surgeon. They investigated two surgeons in the same hospital who had a marked difference in their rates of postoperative wound infections. Both carried a virulent strain of hemolytic *Staph. aureus* in their nasopharynx, but the surgeon whose wounds became infected carried a similar strain on the hands. Tests showed that these organisms passed through the coarse linen (48 threads to the inch) sleeves of his gown, and also passed through holes in his gloves. Punctured gloves proved to be very common, especially in patched gloves. Batiste oversleeves plus close inspection and care of gloves served to prevent infections in patients operated upon by the surgeon bearing the virulent *Staph. aureus* on his hands. The insidiousness of glove punctures cannot be overstressed, since it averaged as high as 24.2% of 6585 gloves, and most of the punctures had escaped the attention of the wearers.

The link between the nasopharynx and the hands as sources of contamination is very close. It is possible that some of the wound infections previously thought to be due to droplet spray from the nose and throat may have come about because the surgeon harbored on his hands the same organism that he carried in his throat. Price⁴⁰ has shown that bacteria with which the hands constantly come in contact may become part of their permanent flora. Gillespie *et al.*¹³ found that 43.4% of a class of medical students were nasal carriers of virulent strains of staphylococci, and 19.5% were skin carriers. Moreover, 12.6%, or 29.03% of the nasal carriers, carried the pathogen both in the nose and on the hands. To assign the cause of an infection to droplet contamination from the nose and throat of the operator *via* the air, one must first rule out the possibility of contamination from the skin of the operator by looking for the same organisms on his hands and looking for punctures in his glove. Just what proportion of infections is due to air contamination and what to the transmission from the skin of the operators remains to be proven. If punctured gloves should be shown to be the worse offender, radiation of air may not be necessary, whereas the practice of wearing extremely thin gloves may have to be changed. It is interesting to recall that Harvey Cushing, who had an extremely low incidence of infection in spite of his lengthy operations, always wore heavy gloves.

Skin of the Patients. More difficult, if not impossible, is the evaluation of the rôle played by the patient's own skin in the production of infected wounds. Although surgeons vary widely in their attempts to clean the skin of the patient and to protect the wound from exposure to it, there is little difference in their reported incidence of wound infection. Some surgeons take great care to cover the exposed surrounding skin of the patient with sterile pads, and paint it with a powerful germicide² while others make no attempt to isolate the skin adjacent to the wound, or to employ anything more in the way of skin preparation than simple removal of grease and dirt with benzene.² Similar results from such a variety of method seem to indicate that the skin of the patient is not as important as some other sources of contamination. The explanation

may lie in the distinction Price^{39,40,41} has demonstrated between two grades of bacterial flora on the skin, namely, the transient and the resident flora. The "transient" flora vary from day to day in quality and quantity since they are composed of bacteria which have settled on the skin from its daily contacts. Therefore, they are scant on clean protected skin, and profuse on dirty, greasy, exposed parts of the body. Since the organisms are frequently imposed on or mingled with other foreign matter, they are easily removed with the grosser contamination in a few minutes scrubbing. The "resident" flora, on the other hand, are remarkably constant for a given individual. The bacteria composing this type are so tightly attached to the skin that theoretically $2\frac{1}{2}$ hours of continuous scrubbing with soap and water are required to remove all of them.⁴⁰ Such adherent organisms would not be easily brushed into the wound by the touch of an instrument or gloved hand, and if the patient's skin is properly freed of "transient" bacteria by adequate scrubbing and applications of germicides, the "residents" become a less important source of contamination. However, no one has been able to prove this contention one way or another, and safety dictates that the surgeon reduce the total flora of the patient's skin to as low a level as possible. This is especially true of exposed parts of the body where the "resident" flora may be partially composed of virulent bacteria as a result of a long contact with sources of these organisms.⁴⁰ Price³⁹ has outlined means of accomplishing this.

Surgical Materials. There is no reason why gloves, dressings, instruments, solutions or sutures should ever be agents for the transfer of bacteria to the wound or from wound to wound. Simple, inexpensive methods for the absolute sterilization of all of these materials have been devised.

Actually, however, these materials do occasionally serve as sources of contamination, since there is widespread discrepancy between available knowledge and current practice. Steam sterilization, for example, is generally regarded as a relatively fool-proof measure. The opinion is current that to insure sterilization it is necessary only to place the material to be sterilized in an autoclave and then to expose it to steam at a given pressure. Actually, there are innumerable details which must be attended to, such as proper wrapping of bundles, proper loading of the sterilizer, and adequate temperature control. When the basic principles of steam sterilization are not understood by those responsible for operating the sterilizer, one sees such dangerous violations as attempts to sterilize materials in sealed glass containers filled with air, attempts to sterilize vaseline and other oily substances with steam, attempts to sterilize tightly packed drums or packages of tremendous size. The most striking recorded example of the difficulties encountered by sterilizer operators who work by ritual rather than understanding is told by Dr. Kenneth Black.⁴ Questioning the efficiency of a steam sterilizer, he placed a thermometer in the center of a tin of dressings. When the temperature of the steam in the sterilizer reached 240° F., that in the tin was only 160° F. Even after he had screwed down the safety valve and sterilized for an hour, the inner temperature was only 220° F. to 230° F. Thereafter, he tested many sterilizers and arrived at similar results with a large percentage. A nurse who did not believe

the thermometers put an egg in the center of each pack in a given sterilizer, and was astonished to find them raw at the end of the customary sterilization period.

Other operating room procedures are subject to the same criticism. There is frequently considerable lag between the available and the applied knowledge. This exists because surgeons have delegated the responsibility of preparing sterile materials for the operating room to nurses who, as a group, do not possess the information necessary to understand such work. The nurses are forced to work by ritual rather than by understanding. When people do not comprehend the reasons for their actions, they are bound to make mistakes, especially when new equipment and new demands require deviation from the standard ritual.

Space does not permit a discussion of the theory and practice of sterilization of surgical material; furthermore, such a discussion is not necessary for there are many excellent papers on this subject, among which may be mentioned those by Hoyt,²⁴ Hoyt *et al.*²⁵ Underwood,²⁶ Walter,^{23,24} Meleney,²³ Spaulding²⁵ and Ecker.^{10,11}

The point which needs emphasis is simply this: methods are available for the preparation of these materials, but they are not being employed, because surgeons by and large are leaving the sterilization of materials in the hands of nurses. If each hospital would appoint one member of the staff to familiarize himself with this subject, not only could many loopholes be closed but considerable money could be saved.

The Sulfonamides. Despite all precautions, bacteria get into clean surgical wounds. In addition, certain surgical incisions must be made into or through infected tissues and are unavoidably contaminated. Consider, for example, a wound through which an acutely inflamed appendix is removed. Accidental wounds are obviously nearly always contaminated with bacteria, though not necessarily with virulent types.¹⁶ Thus there are three types of wounds in which bacteria are usually present and in which infection may and often does develop. The spectacular success of the sulfonamides in the treatment of certain established infections suggests that they might be employed to prevent infection of these wounds by their contaminating organisms.

The bacteria which are involved in the majority of surgical infections may be listed as follows: *Staph. aureus*, *Strep. hemolyticus*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas pyocyanea* and anaërobic spore-forming bacilli.

Except in the case of *Strep. hemolyticus*, the systemic administration of sulfonamides while of some benefit has not been remarkably successful in the treatment of infections caused by these organisms. Would the prophylactic administration, either locally, systemically or in combination, be more effective? The mass of evidence both experimental and clinical which has accumulated in the attempt to answer this question is too vast to be reviewed here. Those who are interested must consult such papers as those of Reed and Orr,²⁷ Colebrook and Francis,²⁸ Hawking,^{29,31} Pickrell,³² Bonnin and Fenner,³ Long and Ravdin,³³ Jensen *et al.*,³⁴ Throckmorton,³⁵ Harbison and Key³⁶ and Key.³⁷

In spite of the volume of work that has been done, the problem has not been solved. The evidence seems to show, however, that the prophylactic use of the sulfonamides, especially locally, is of definite

benefit in preventing infection with at least some of the bacteria which commonly cause wound infection and when properly used do not interfere with normal wound healing.

The local administration is based upon the supposition that it will result in a higher concentration of a given sulfonamide in the wound than can be obtained when it is administered systemically only.

When a sulfonamide is administered systemically, the concentration in the wound is approximately that of the blood and since it is not safe to keep this above 10 to 15 mg. per 100 cc.; the concentration in the wound cannot exceed this amount. The concentration of a given sulfonamide which can be obtained in a wound is directly proportional to its solubility in tissue fluids and the length of time that concentration can be maintained is inversely proportional to its solubility in tissue fluid. Thus sulfanilamide which is extremely soluble provides a high local concentration for a short time while sulfathiazole or sulfadiazine, which are relatively insoluble, will provide a lower local concentration which persists for considerable time.

Hawking^{20,21} has shown that sulfanilamide is absorbed and disappears from a wound in less than 24 hours, while sulfathiazole persists 4 or 5 days. Sulfadiazine remains in a wound even longer.

It has also been shown that sulfanilamide will diffuse slowly through dead tissue, but that sulfathiazole does this at an even slower rate. Furthermore, the high local concentration of sulfanilamide exists for only a few millimeters about the wound, for as soon as the drug reaches tissue with an intact circulation, it is "whisked" away and its local level becomes that of the body as a whole.²¹

These considerations dictate that in practice it may be well to employ a mixture of sulfanilamide and sulfathiazole or sulfadiazine. The sulfanilamide provides a high local concentration for a short time plus fairly rapid penetration of dead tissue. The other component serves to maintain a lower concentration over a period of several days. Whether sulfadiazine or sulfathiazole should be used is not established, but the evidence seems to be in favor of sulfathiazole.^{20,44}

That the high local concentration which can be obtained by placing these drugs in wounds will serve to extend their range of usefulness beyond that already established by systemic administration remains to be demonstrated conclusively. At present the evidence seems to show that it will.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

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AVIATION OPHTHALMOLOGY.

THE experiences of the early years of the last war made evident the fact that not all soldiers were physically and mentally equipped for flying. According to Armstrong¹ (1936), it was noted that in some instances as many as 50% of the candidates for the air services suffered

from a neurosis during training. It was also noted that 90% of the accidents to graduate pilots were due to defects in the pilots themselves. Others have mentioned that of the remaining 10%, 2% were due to enemy action and 8% to plane defects.

These observations naturally led to the formation of medical units, both for pilot examination and for research in aviation medicine. Because of this development, the percentage of accidents due to pilot error in the Royal Air Force had been reduced to 60% in 1941. Following the last war, interest in research lagged, but in more recent years an increasing amount of work is being done. Some of this has related to aviation ophthalmology and an attempt will be made briefly to review part of it here. The increased speed, high altitude capabilities and the general importance of air power in the war have been the stimuli for much of this work. Despite the many changes, the standards for pilot qualification set up by Wilmer²⁴ and his coworkers are, in the main, still satisfactory. They also contributed many of the basic facts in research from which more recent work has evolved.

Visual Acuity. These standards for the armed forces remain at normal, or 20/20 vision, for new candidates. In civil aviation the tendency has been to lower these standards and the wearing of glasses is permitted. The trend would seem to be toward a further lowering of the standards for initial visual acuity where vision can be improved to normal with glasses. Visual acuity of 20/50, correctible to 20/20 in each eye, is now the minimum vision without glasses required for transport pilots. For private pilots, if the visual acuity is less than 20/50 it must be correctible to 20/30. In regard to visual fields, the confrontation method is required in civil examinations, while a more extensive examination is done by the armed forces at entrance.

Hayden and Goss⁸ have reported that at the U. S. Naval Academy the average incidence of visual deficiency has been decreased from 8.18% (classes 1934 to 1940) to 2.86% (classes 1941 and 1942) by requiring some hyperopic reserve in all the candidates accepted. This has markedly reduced the number who have become myopic before graduation and whose training is wasted from the standpoint of the Government. About 1 diopter of hyperopia is the preferred amount in a candidate; over 2 diopters disqualifies. These observations are of interest where young adults are to be given expensive and time-consuming training in work which, for its pursuance, requires normal visual acuity.

A general darkening of the visual field is noted with anoxia. If oxygen is then given, a sudden brightening of the field follows. This is a universal observation. Beginning with Wilmer and Berens in 1918, a number of observations by various investigators were made on the effects of visual acuity of anoxia. The findings were variable. Recently McFarland and Halpern¹³ found that changes in visual acuity with anoxia at high illuminations were negligible, while there was a large drop in foveal visual acuity at low illuminations. Their conclusion was that "so far as foveal visual acuity is concerned . . . it is much more important that airplane pilots be provided with oxygen on night flights than during daylight flights." Work is now under way to determine at what level oxygen should be used during night flights.

Depth Perception. The importance of good depth perception to a flyer is obvious, and even with the best visual acuity and muscle balance, landings under certain conditions, such as on snow and water, may be hazardous. The factors involved in depth perception are well understood and are usually grouped into those inherent in the individual and those dependent on his environment and his past experiences with it. At the start of the last war, attempts were made to measure this ability by using the stereoscope in near vision. This was found to be unsatisfactory and, later, the Howard Dohlman apparatus was introduced and is still in use. This apparatus is stationed at a distance of 20 feet from the examinee and is an excellent test for stereoscopic vision at a distance. When used properly, it determines his inherent degree of ability to judge distance.

The known factors in faulty depth perception, as listed by Thorne,²⁰ are: (1) inequality of vision; (2) accommodative asthenopia; (3) heterophoria; and (4) convergence insufficiency. Using the Howard Dohlman apparatus, Deyo⁶ found depth perception to be only 20% as accurate with one eye covered as with the use of the two eyes. This illustrates the disadvantage under which a pilot with only one eye or with strabismus labors.

That aniseikonia, or inequality in the image size of the two eyes, may affect depth perception unfavorably is easily demonstrated. That it is commonly a cause of poor depth perception as usually tested is very doubtful. With the testing of large groups of individuals with the Howard Dohlman apparatus, the ones who are not within normal limits almost invariably reveal defects in their ocular muscle balance, refraction or visual acuity which readily explain the difficulty.

Walker²¹ recently investigated the superiority of binocular over monocular vision in depth perception in respect to the vertical or horizontal position of the stimulating object. He used an apparatus designed by himself with two 0.125 inch rods 2 inches apart at 22.5 feet from the eye piece. Both rods were movable by the turning of a wheel by the subject. His conclusions were: (1) binocular vision is superior in perception of depth when the stimulus is in a vertical position or at an angular displacement of not over 60°; (2) when the visual stimulus is horizontal the error of perception is as great for binocular vision as for monocular vision; and (3) under ordinary visual conditions secondary depth perception factors such as relative size, interposition and relative height above the line of vision apparently compensate for the lack of retinal disparity that is present when objects are horizontal. In another study, Walker²² compared movement of the stimuli by hand and mechanically but did not find enough correlation to suggest that the mechanical was superior to the Howard Dohlman or hand type. His studies do not controvert the known facts in regard to depth perception.

Good muscle balance is of great importance to a pilot. If he has a high degree of esophoria, exophoria or hyperphoria, while he may see and judge depth fairly well under ordinary conditions, if fatigued he may suppress the vision of one eye or suffer from diplopia, usually the former. If he suppresses, his depth perception then becomes similar to that of a one-eyed person and is much inferior. If he suffers from actual diplopia, the results might easily be disastrous. The Army regulation

in this regard have been that depth perception must average 30 mm. or less on the Howard Dohman apparatus. Esophoria (at 20 feet) of more than 4 diopters, if associated with a prism divergence of less than 4 diopters, disqualifies. Esophoria of over 10 diopters disqualifies even if diverging power is equivalent. Exophoria of more than 5 diopters disqualifies. Hyperphoria of more than 1 diopter disqualifies. An angle of convergence of less than 40° disqualifies. Gross deficiencies, such as strabismus and diplopia (except in extreme rotation) naturally disqualify.

Color Vision. This is of importance to any pilot because of the use of color in navigation lights, and it is of even more importance to the military pilot because of the use of Very pistols, flares and so forth in his work. The Ishihara test, or similar pseudo-isochromatic plates, is the most reliable for detecting all degrees of color blindness. Color blindness is detected in this test very frequently in individuals who had no previous knowledge of a defect. If a defect is found, the Holmgren yarn test is then generally used and, being much less delicate, eliminates only a few of those found by the Ishihara test and these have the more gross forms of color blindness. If the Holmgren test is passed, they are acceptable.

This method appears to work very satisfactorily as regards civilian and transport pilots. With reference to military pilots, White's²³ findings are of interest. We found that individuals color deficient as revealed by the Ishihara plates but able to select gross shades of red and green were deficient in 3 of the main requirements of the military pilot with reference to color vision, namely, recognition of Very pistol signals, navigation lights and map color shades. He found that navigation lights on a plane could be identified 1 to 4 miles farther away by normals than by the Ishihara failures.

The most recent review of color vision as it affects military fliers is that of Schwichtenberg.¹⁷ He reviews the Young-Helmholz and the Edridge Green theories of color vision, gives the correct technique for the Holmgren yarn test and suggests a technique for the Williams lantern test which he feels simulates conditions of military operation more closely than do other tests of color vision. He advocates this latter technique, especially for testing questionable cases.

A common suggestion in regard to this problem has been that numbers be substituted for or added to colors as signals. That is, all green lights be made double lights, red lights single, and so forth. This, of course, is not at all feasible from the military viewpoint where colors have a multiplicity of uses. It might be possible with civilian aviation, but here, too, we have numerous signals and navigation lights, on and off the ships, which would make it a very difficult problem, and there are many more urgent ones at the present time.

As far as we have been able to determine, color blindness is of no aid in penetrating the usual types of camouflage. When one considers that if a landing field is next to a pasture which appears green from the air the landing field will be colored likewise, it can be seen that this offers no advantage to the color blind.

Black Out. Blacking out is well described by Ryan.¹⁶ This is due to the blood gravitating downward from the pilot's head. It may occur when coming out of a dive, making a sharp turn, accelerating, and so

forth. It results in partial or complete loss of vision and the pilot may see anything from a red glare to complete darkness. The latter may be accompanied by unconsciousness, this occurring usually when forces greater than 4 G. are produced. ("G" refers to the acceleration due to gravity.) For instance, the effective weight of a 150 pound pilot at 4 G is 600 pounds. The first effect of G. is the feeling of being pushed into the seat of the machine, then of the abdomen being pressed downward. Then the visual fields begin to dim, this being followed by complete loss of vision, followed in some cases by unconsciousness. This will last up to 5 seconds, depending on the amount and duration of G. and the response of the pilot's vascular system to it.

Ryan¹⁶ also mentions that it has been the experience of the British that pilots with low blood pressures react badly to abnormal movements in the air. Young²⁶ analyzed 159 fatal crashes and concluded that hypotension may be the underlying cause in many cases of pilot failure. Seventy-three pilots (45.9%) manifested some form of hypotension (a blood pressure of less than 110 systolic or 70 diastolic); of these, in 62 (85%) the official cause of the crash was pilot error. On the other hand, only 43% of those with normal blood pressure were involved in crashes charged to pilot error. Reports from England are that for every 4 pilots killed in combat, 6 lose their lives because of some other cause at home.

Young²⁶ states also that "if enough violent flying is indulged in, permanent damage can be done to the central nervous system as was witnessed a few years ago when 2 fatalities occurred on one of the larger aircraft carriers within a few hours after carrying out an extensive dive bombing exercise." In this regard, we observed a test pilot several years ago who had developed a right third nerve paralysis 2 days after making an exceedingly rapid ascent in a plane he was testing. The condition was improving rapidly when we observed him and he revealed no other central nervous system disturbance despite an extensive examination. He was advised to limit his activities but a short time later was killed in a crash the cause of which was obscure. His blood pressure when examined here was 120/70 on a single reading, and on this single reading he could not be classed as a hypotensive. However, one might conclude that once a vascular accident, no matter how minimal, has occurred in a pilot he should be grounded.

Dark Adaptation. Several years ago a number of articles appeared^{13,14,15} suggesting that night blindness due to vitamin A deficiency was relatively common in the general population and could readily be produced experimentally. A large amount of literature on the subject has since accumulated^{15,19} and the consensus among most ophthalmologists at present is that it is not common and that it is not readily produced by dietary restriction. In fact, other changes may occur, as in the skin, with no definite findings as regards the dark adaptation. Recently, Yarbrough and Dann²⁵ found no correlation between dark adaptation readings and the blood level of vitamin A. They suggest that blood determinations of vitamin A seem to be the most promising method of detecting mild avitaminosis A.

The following reports would seem to indicate that as regards pilots under ground conditions, poor dark adaptation is a negligible factor. This is not true, of course, under conditions of anoxia, as will be mentioned elsewhere.

Eighty pilots from a commercial air line were examined here by Sheard.¹⁸ While the threshold was higher for a few than the mean for the group, none could be considered abnormal. The changes found for the most part could be correlated with the pilot's age. In none was there change enough to warrant a recommendation against night flying. That these were normal variations is further shown by the fact that there was no significant change following months of increased intake of vitamin A. Porter, Carlson and Henton¹⁵ examined 65 pilots on the Birch-Hirschfeld photometer; none were found deficient. They then examined 34 non-fliers and found 1 below the minimum standard. Following this they examined the same group, using a luminous clock to get a rough estimate of dark adaptation; their results corresponded very well with the photometer readings. Now that we know that poor dark adaptation is not common in the general population, perhaps if any testing involving large groups is to be done at all, this method or a modification might be satisfactory. As far as is known, no routine testing of the dark adaptation of military pilots is now done.

Anoxia. As the brain, especially the cortex, is very sensitive to changes in oxygen tension, it is not surprising that the eye should react in a like manner. The circulation is similar and the optic nerve is essentially an extension of the white matter of the brain.

I shall enumerate briefly here a few of the changes which take place with anoxia as regards the eye and refer any one particularly interested in the subject to an excellent review recently published by McFarland, Evans and Halpern^{12,13} which has a complete bibliography appended.

Among the ocular changes observed are exaggeration of muscle imbalances, a decrease in the range of accommodation and other effects which one generally associates with fatigue reactions of the central nervous system. In this regard, by photographic studies, McFarland, Knehr and Berens^{14a} found that it not only took longer to read a given line but that the eyes did not coördinate as well at 18,000 feet. They also found that known muscle imbalances were greatly accentuated during anoxia^{14b} and that the precision of ocular reactions in this was diminished. Other changes are: impairment of dark adaptation (Berens²), widening of the angioscotomata in the central visual field (Evans and McFarland⁷) and an increase in the caliber of the retinal arteries and veins (Cusick, Benson and Boothby⁴). With the administration of oxygen there is a tendency in all these effects to quickly return to normal, and if the oxygen is continued, in the case of the retinal vessels, they become measurably smaller than normal. Some of these changes due to anoxia may be noted at altitudes as low as 5000 feet but are much more obvious at heights of 18,000 feet and over. The occurrence of aëroembolism in the retinal vessels has not been reported to our knowledge.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*etc*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal of the American Medical Association* with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is *under consideration* or *being meditated upon*, i.e., that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the correct meaning.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

SEPTEMBER, 1942.

ORIGINAL ARTICLES.

EXPERIMENTAL BUNDLE BRANCH BLOCK AFTER ABLATION
OF ONE OR BOTH VENTRICLES.*

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NUMEROUS references to bundle branch block in medical literature, as well as critical discussions, are available in the excellent monographs by Wahlin,¹⁴ Mahaim,¹¹ and Yater.¹⁷ In spite of much experimental work,^{1,9,13,15,16} there is still extant a belief that there is a difference between the electrocardiographic picture produced by a lesion of a bundle branch in a dog or cat and that produced by disease in man. Yater,¹⁷ for instance, writes (p. 2): "This difference is explained by the differences in the anatomic course of the left bundle branch, the axis and position of the heart, the shape of the heart, and the thickness of the two ventricles."

If one dissects the ventricular muscle bundles of various species commonly used in physiologic studies, the arrangement is found to be very similar in dogs, cats, rabbits and monkeys; and this, in turn, is similar to that found in pigs, cattle and sheep. Much of our supposed knowledge of the conducting system is that obtained from study of ungulate hearts.

Because of these anatomic similarities in various families of mammals, it seemed necessary to reinvestigate the question of localization of branch bundle block, which in laboratory animals is said to be different from that of man, due to supposed anatomic dissimilarities.

* Supported by a grant from the Hendricks Research Fund of Syracuse University College of Medicine.

Method. Twelve animals (dogs, cats, and rabbits) were anesthetized with soluble pentobarbital, artificial respiration instituted, the thorax opened and the pericardium slit. A superficial stitch, taken through fat and epicardium at the apex, anchored it to the chest wall to prevent shift of the anatomic axis. Three standard limb leads were recorded simultaneously on research galvanometers built by the Cambridge Instrument Company, the technique being the same as for clinical electrocardiography. After a control record was taken, first a part, *e. g.*, either the anterior or the posterior section, and later all of the free wall (*i. e.*, not including the septal portion) of one or other ventricle was completely removed. If we applied M/5 solution of potassium chloride to the exposed septal surface, conduction through the exposed bundle branch could be eliminated. Finally the free wall of the opposite ventricle was removed, leaving the isolated septum alone with but one of its sides visibly contracting. No effort was made to control hemorrhage. Some of the blood was taken up with cotton pledgets, and later clots were removed. To our surprise, hemorrhage was not excessive, and in view of the absence of both coronary and systemic circulation, the survival time of the unloaded heart in such preparations was sometimes 20 to 30 minutes (average, 15). We wish to stress that only the narrow posterior edge of the heart was in direct contact with the mediastinum, since the supporting stitch maintained the normal position of the septum. Hence the cardiac surface in contact with other tissues decreased as the experiment proceeded.

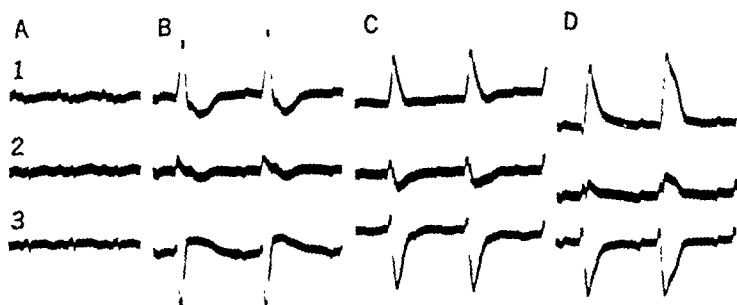


FIG. 1.—Left branch bundle block and left axis deviation produced in absence of left ventricle. In all records 1 mv. = 1 cm. Heavy time lines = 0.1 second. Three standard limb leads from a rabbit: A, Normal control; B, after the anterior wall of left ventricle is cut away; C, after all the rest of the left ventricular wall is cut off; D, later, right ventricle still beating regularly.

Results. Observations, which were similar in all species studied, are best presented by reproduction of the electrocardiograms themselves. Figure 1 shows the progressive changes when the entire free left ventricular wall was removed. Figure 2 shows the effect of removing the right ventricular free wall and applying M/5 KCl to the right septal surface in (A) a rabbit, (B) a dog, and (C) a cat. Figure 3 demonstrates the effect of removing free walls of both ventricles and later applying M/5 KCl to the right septal surface. One must remember that more than one variable is at hand in this type of experiment. Anoxemia and cooling play a part as well as removal of areas. Hence it is obligatory to employ simultaneous recording to make certain that all external conditions are exactly

alike for each lead at a given instant. When anoxemia affects the whole heart, fibrillation is prone to occur. In septal preparations, terminal fibrillation is uncommon.

Discussion. The earlier German investigators, Sir Thomas Lewis,¹⁰ and more recently Nahum, Kisch, Hoff, and Kaufman,¹² have stated that the normal electrocardiogram was a summation of one dextro- and one levo-cardiogram derived from the respective ventricular surfaces. The latter group have also stated that Lead 1 is a summation of anterior left and posterior right ventricular forces,

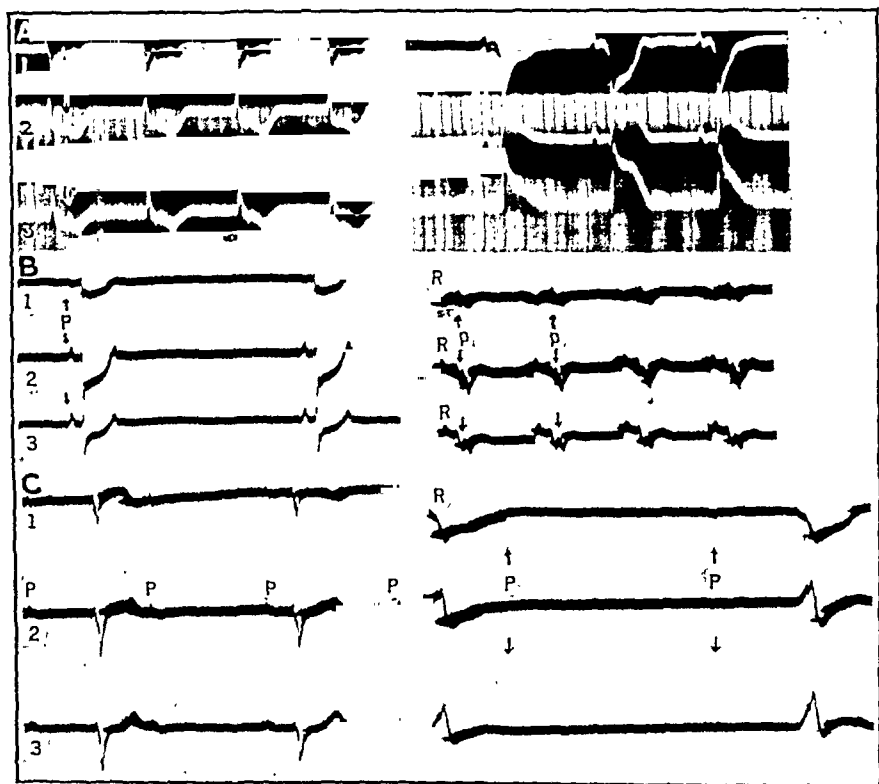


FIG. 2.—Right bundle branch block and right axis deviation in the absence of the right ventricle. Three standard leads of (A) rabbit, (B) dog, and (C) cat, taken after removal of the entire right ventricular wall, before (left column) and after (right column) application of M/5 KCl to the exposed right side of septum. Note that these changes in the S-T are independent of rhythm.

Lead 3 a summation of posterior left and anterior right. Certainly this cannot be the explanation of either Lead 1 or Lead 3 when anterior and posterior surfaces of both ventricles are entirely removed. In neither ventricle of *mammals* does removal of the anterior wall produce the same change as does removal of the posterior wall (see Fig. 4). Furthermore, it is difficult to understand how the S-T of Leads 2 and 3 (right column, Fig. 2) could be elevated by effects from the right ventricle posteriorly when in our experiments its whole free wall is cut away and the right septum treated with M/5 KCl.

It is usually accepted that an action current in the main bundle does not record on the standard leads. (See Bazett,³ p. 284; Ashman,² p. 62.) It is not specifically stated whether action currents in the bundle branches *per se* influence the electrocardiogram or whether interruption of these pathways influences the electrocardio-

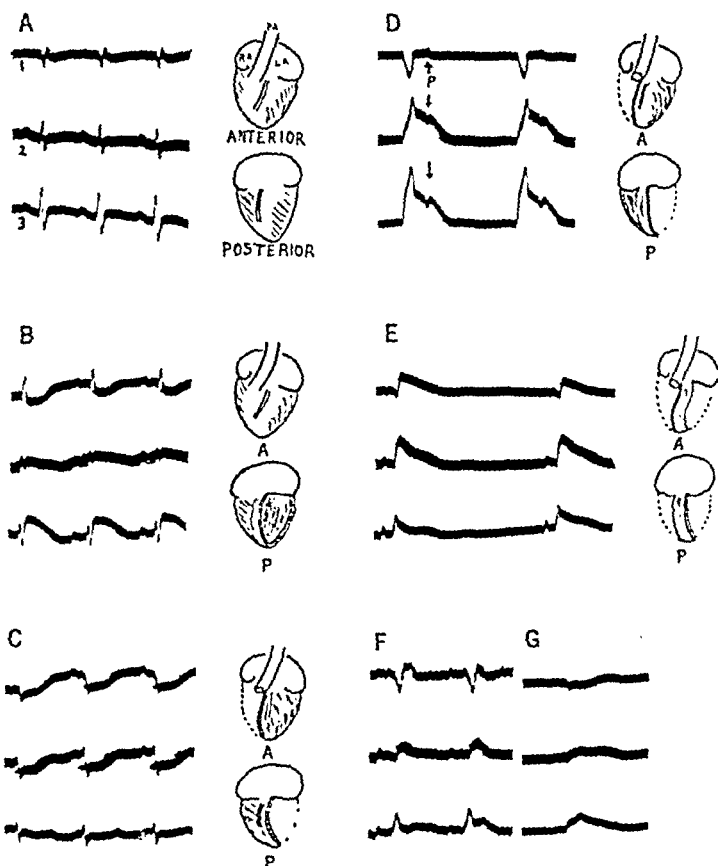


FIG. 3. Isolated septum. Standard limb leads from a rabbit: A, Control; B, after removal of right posterior ventricular wall; C, after removal of whole free right ventricular wall; (D) removal of posterior left wall; (E) removal of rest of left ventricle. Only the auricles and septum remain and these are beating regularly and *exactly*. F, After application of 0.5 M KCl to the right septal surface; G, same as F but much later. Line drawings show portions of heart present when each record was taken.

gram by preventing the excitation of the lateral muscle masses. If one removes all of both ventricular walls and the contracting septum alone remains, a complete electrocardiogram is obtained whose amplitude is greater than that of the control record.

The widening of QRS found in branch bundle block by earlier authors (e. g., Lewis) was explained by supposing that there was

rapid transmission along the conducting tissue of the uninjured side followed by circuitous transmission *via* ventricular muscle back to the injured side. Obviously, the great widening of QRS seen in Figure 1 cannot be so explained. That *anoxemia* is the cause of only a part of the slowing seems probable, as the S-T is often greatly widened when there is little or no P-R prolongation (Fig. 1B, Fig. 2B and Fig. 3C and E); if A-V conduction is unaltered, why should septal conduction be affected by this same condition?

It has been stated by Cardwell and Abramson⁴ (also DeWitt⁷ and King⁸) that the upper septum does not receive primary branches from the main bundle of the conducting system but that on the right side the Purkinje fibers pass to the apex along the moderator band, then turn back again toward the base to supply both the free walls and the septum. Others, Curran,⁶ Cohn,⁵ Mahaim,¹¹ have described a supply to the septum from higher levels of the right

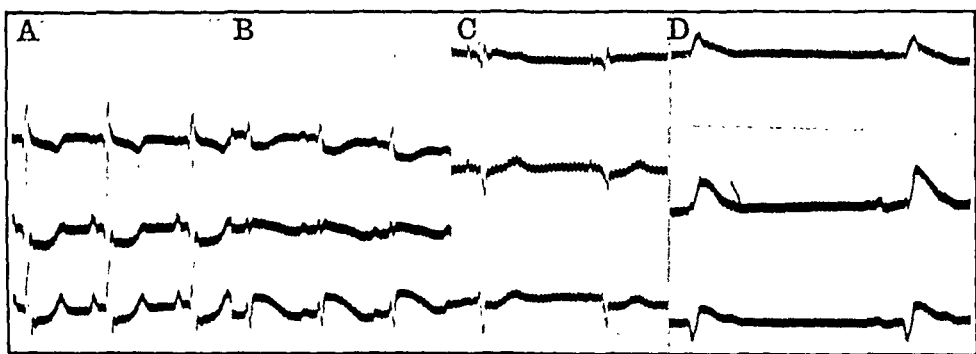


FIG. 4.—A, Three standard leads from a rabbit in which the anterior wall of the right ventricle only had been removed. B, Same in another rabbit where the posterior wall of the right ventricle only had been removed. C, Same in a third rabbit where the anterior wall of the left ventricle only had been removed. D, Same in a fourth rabbit where the posterior wall of the left ventricle only had been removed.

branch. Cardwell and Abramson do describe septal subdivisions of the left crus and add: "... one of the larger fasciculi may even arise from the posterior or anterior papillary division rather than from the main left crus."

DeWitt⁷ writes in regard to the left branch: "About 2 mm. beyond the point of division the posterior branch gives off 2 long slender branches to the septal wall which anastomose with branches from a septal branch of the anterior division to form a septal plexus (p. 484-5). . . . The septal wall of the left ventricle both between the papillæ and where it curves around behind the papillæ is covered by a network of Purkinje fibers, similar to the network described on the papillæ and formed by the anastomosing subdivisions of septal branches of the anterior and posterior divisions of the main limb which have already been described."

"... occasional small branches pass back from the anterior and posterior papillary plexuses to the septum and join with the septal

branches to form the septal plexus. The plexus described covers well the septal surface to the level of the branching of the main left limb and even sends some fine filaments higher on the septal surface."

Thus on the right side of the heart several authors state that the main bundle and the right crus give off no basal septal branches, but believe that the septum is activated from recurrent branches. On the left, DeWitt seems to describe mainly recurrent branches, while Cardwell and Abramson describe both direct septal supply from the left crus and recurrent papillary and septal fibers from the plexuses on the walls.

We find both sides of the isolated septum in three families of mammals contracting coördinately, following an S-A rhythm, although any recurrent pathways curving back from the papillary muscles would have been interrupted by removal of the right and left lateral walls. When KCl is applied to one side of the exposed septum, records similar to those diagnosed clinically as complete branch bundle block appear which are discordant and which agree with the American terminology. Failure to control *all* conduction to one side of the heart is probably the explanation of the confusion in the literature as to localization of branch bundle block in laboratory animals.

Conclusions. 1. In order to record a QRS-T complex, the presence of the "free" (*i. e.*, non-septal) walls of either (or both) right or left ventricles is unnecessary.

2. Not even the right side of the septum depends entirely for its excitation on conduction pathways which first reach the papillary muscles at the apices and then turn back. It contracts with a normal S-A rhythm when such pathways are interrupted by the total ablation of the "free" portions of both right and left ventricles. *i. e.*, impulses are conducted from the main branches directly to the septum.

3. These experiments have not proven definitely whether the electrocardiograms recorded from the isolated septum are due to excitation of the septal muscle alone or whether action currents passing in the right and left branches (whose peripheral expansions were amputated) also produce some effect.

4. Not only does electrical activity of the free wall of each ventricle affect the electrocardiogram, but various portions of each wall have a characteristic effect.

5. These experiments do not support the theory that an electrocardiogram is summation of only one dextro- and one levocardigram.

6. That the amplitude of deflections increases when the contact surface of the heart diminishes suggests that normally there is considerable neutralization of current.

7. So-called "axis deviation" appears when less rather than more of a given ventricle is present. Hence it appears to be due to loss of electrical components, with consequent change in the algebraic sum.

8. Laboratory animals, dogs, cats and rabbits, conform to the newer or American terminology for bundle branch block; *i. e.*, when the right side of the heart is anatomically and functionally absent, there is a deep wide S_1 and a tall wide QRS_3 . The reverse is true for anatomic and functional absence of the whole left ventricle.

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ACUTE BACTERIAL ENDOCARDITIS OF THE TRICUSPID VALVE.

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ACUTE right-sided bacterial endocarditis is admittedly rare both clinically and pathologically. An autopsy done at Jewish Hospital on a case of pneumococcic tricuspid valvulitis prompted us to determine the frequency of tricuspid involvement, and to review the

autopsy records of the Philadelphia General Hospital.* A search of the literature revealed a marked difference of opinion concerning the incidence of tricuspid valve infection.

Osler,⁷ in 1885, stated that the right heart was rarely infected alone and reported tricuspid involvement in only 5 of 200 cases of malignant endocarditis. Preble⁹ stated in 1904 that 8.5% of all cases of pneumococcic endocarditis were limited to the tricuspid valve. Horder¹ reviewed 118 necropsies of infective endocarditis.



FIG. 1—Note the granular, strawberry-like vegetation having a broad base on the tricuspid valve. (Jeff. Hosp. Mus. NA530; Phila. Gen. Hosp. No. 25000.)

finding none restricted to the tricuspid valve. Many of these earlier reports probably included cases of subacute bacterial endocarditis, for prior to Libman's³ investigation in 1910, no division between the acute and subacute forms was made. Libman stressed the advisability of maintaining a distinction between the two forms, even though a sharp dividing line was not always possible. Thayer¹¹

* We wish to thank Dr. Jefferson W. Clark, Director of the Laboratory of the Philadelphia General Hospital, for his permission to review the records.

in 1926 found only 2 of 362 cases were limited to the tricuspid valve, but in 1932 reported right-sided involvement in 10 of 185 cases of acute bacterial endocarditis. Phipps⁸ in 1932 reported 44 cases of acute bacterial (non-pneumococcal) endocarditis of which 3 involved the tricuspid valve alone. Among 23 cases of pneumococcic endocarditis at the Massachusetts General Hospital, Lord⁶ found lesions restricted to the right heart in 3 cases. Ruegsegger¹⁰ reported 19 cases, an incidence of 2.9%, of acute pneumococcic endocarditis



FIG. 2.—Several elongated, pedunculated vegetations project from each of the tricuspid leaflets into the right ventricle. (Jeff. Hosp. Mus. NA530; Phila. Gen. Hosp. No. 25000.)

among 665 cases of pneumococcic infection. One case of tricuspid and 1 of aortic and tricuspid involvement occurred in the 15 cases of acute pneumococcic bacterial endocarditis that came to autopsy. In contrast to the above reports, Libman^{4,5} stated that 27% of his cases of bacterial endocarditis involved the right heart.

Our own studies were taken from the autopsy records of the Philadelphia General Hospital from January 1, 1920, to December 31, 1940. Among 26,007 autopsies, there were 646 cases of acute bacterial endocarditis, an incidence of 2.5%.

In Table 1 are listed the number and percentage of cases involving the different valves. The mitral valve was by far the commonest seat of acute bacterial involvement with the aortic valve next. Only 20 cases (3%) were limited to the tricuspid valve and 5 cases (0.8%) to the pulmonic valve. If we include those cases in which the tricuspid and pulmonic valves were affected in association with left-sided endocarditis, vegetations in the right chambers of the heart were present in 53 cases (8.2%).

TABLE 1.—INVOLVEMENT OF VALVES IN ACUTE BACTERIAL ENDOCARDITIS (ALL TYPES OF ORGANISMS).

	No.	%.
Mitral valve, alone	308	47.6
Aortic valve, alone	164	25.4
Mitral and aortic valves	121	18.7
Tricuspid valve, alone	20	3.1
Mitral and tricuspid valves	10	1.5
Aortic, mitral and tricuspid valves	7	1.1
Pulmonic valve, alone	5	0.8
Aortic and tricuspid valves	5	0.8
Mitral, pulmonic and tricuspid valves	3	0.4
Mitral, aortic, tricuspid, pulmonic valves	3	0.4
Total cases	646	100.0

Preble⁹ and others^{2,13} have pointed out that the pneumococcus attacked the tricuspid valve more frequently than other organisms. We therefore determined how often the tricuspid valve was affected in lobar pneumonia.

Of the 26,007 cases autopsied, 1041 were cases of lobar pneumonia. Sixty-two (5.9%) of these revealed acute bacterial endocarditis. This approximates the figures of Lord⁶ (4.15%) and of Preble,⁹ who stated that 1% of all pneumococcic pneumonias and 5% of all fatal cases had acute pneumococcic endocarditis.

TABLE 2.—INVOLVEMENT OF VALVES IN FATAL ACUTE PNEUMOCOCCIC BACTERIAL ENDOCARDITIS.

	No.	%.
Mitral valve, alone	23	37.0
Aortic valve, alone	18	29.0
Tricuspid valve, alone	9	14.5
Mitral and aortic valves	5	8.0
Aortic and tricuspid valves	3	4.8
Mitral, aortic, tricuspid, pulmonic valves	2	3.2
Mitral, aortic, tricuspid valves	1	1.6
Mitral, pulmonic, tricuspid valves	1	1.6
Total cases	62	100.0

In Table 2 are listed the various valves involved in pneumonia. Of the 20 cases previously mentioned in which the tricuspid valve was involved alone, 9 (45%) were due to the pneumococcus. It appears that the pneumococcus attacks the tricuspid valve more frequently than other organisms. If we separate the cases of pneumococcic endocarditis from the group as a whole, we find that 9 of

62 cases of pneumococcic endocarditis or 14.5% occurred on the tricuspid valve alone, but only 11 of 584 (1.8%) of all other cases of acute bacterial endocarditis were restricted to the tricuspid valve.

As much as the records permitted, we reviewed the 20 cases of tricuspid endocarditis (Table 3). One thing that impressed us particularly was the unreliability of physical findings upon cardiac auscultation. In but 8 of the 20 cases was mention made of any murmur being heard, and in none of these was it heard specifically over the tricuspid area. Of the 8 cases, 4 had systolic murmurs over the mitral or apical area, in 2 double mitral murmurs were heard, and 2 exhibited aortic murmurs.

TABLE 3.—ACUTE BACTERIAL ENDOCARDITIS OF TRICUSPID VALVE ALONE.

Primary disease.	Auscultatory phenomena.
1. Septicemia
2. Pneumonia
3. Lobar pneumonia	Systolic precordial murmur
4. Lobar pneumonia
5. Postpartum sepsis	Rough apical systolic murmur
6. Lobar pneumonia
7. Lobar pneumonia	Apical systolic murmur
8. Suppurative prostatitis
9. Bronchopneumonia	Double mitral murmur
10. Streptococcic septicemia	Apical systolic murmur
11. Lobar pneumonia
12. Erysipelas	Aortic systolic murmur
13. Puerperal sepsis
14. No diagnosis
15. Bronchopneumonia
16. Lobar pneumonia
17. No diagnosis	Double mitral murmur
18. No diagnosis	Mitral systolic and double aortic murmurs
19. Lobar pneumonia
20. Staphylococcic septicemia

Keefer,² Preble,⁹ and others^{1,13} have mentioned that physical signs of acute bacterial endocarditis may be lacking. Most authors attribute this to the fulminating course of the disease. One of us (S. B.) has recently studied 2 cases of acute bacterial endocarditis, 1 due to pneumococcus Type VII involvement of the tricuspid valve, and the other streptococcus hemolyticus infection of the mitral valve. Both patients died after 5 weeks and were examined post-mortem. Despite the fact that the diagnosis was made clinically and these patients were repeatedly examined for auscultatory cardiac changes, no murmurs were heard. Figures 1 and 2 are photographs of 2 cases of acute bacterial endocarditis of the tricuspid valve. They indicate how large these vegetations may be without producing cardiac murmurs.

The etiology and pathogenesis of cardiac murmurs is still a very fertile field for investigation. Most observers feel that acute bacterial endocarditis is frequently apt to strike valves that have not been the seat of previous inflammatory processes. If that is the case, it may be that the amount of damage to the chordæ tendineæ and

valve itself is of more importance in the production of murmurs, than the size or location of the vegetations. We would like to emphasize the fact that absence of auscultatory changes should not eliminate a diagnosis of bacterial endocarditis. From our experience, the continuance of a positive blood culture in pneumonia longer than a week should make one suspect the presence of acute bacterial endocarditis.

Summary. 1. In 26,007 necropsies there were 646 cases of acute bacterial endocarditis, an incidence of 2.5%.

2. The mitral valve, singly, was most frequently involved (47.6%), followed by the aortic valve, singly, (25.4%), mitral and aortic (18.7%), and tricuspid, singly, (3.1%).

3. Lesions were limited to the tricuspid valve in 20 cases, an incidence of 3% of acute bacterial endocarditis and 1 out of 1300 autopsies.

4. Right-sided bacterial endocarditis occurred in 8.2% of the cases.

5. Lesions involved the tricuspid valve alone in 9 of the 62 cases of pneumococcic bacterial endocarditis (14.5%).

6. The lack of diagnostic auscultatory findings in acute bacterial endocarditis of the tricuspid valve is emphasized.

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THE INCIDENCE OF ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS IN CONGENITAL HEART DISEASE.

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THE outstanding work of Maude Abbott on congenital heart disease during the past 25 years has greatly clarified the diagnostic features of the individual cardiac anomalies, and made it less neces-

sary to resort to the general term "congenital heart disease." Other investigators have thus been stimulated to submit case studies and statistical analyses that have cast considerable light on their course, prognosis and complications. Recently, the encouraging results obtained through the surgical treatment of patent ductus arteriosus and the hope of thereby decreasing the frequency of fatal complications have also served to attract increasing attention to a field of medicine that was long regarded as rather futile from the standpoint of therapy.

This study is concerned primarily with one phase of this broad subject, namely, the incidence of acute and subacute bacterial endocarditis and endarteritis in hearts that are the sites of congenital defects. We are not discussing the embryology and pathologic anatomy of the cardiac anomalies, nor the clinical and diagnostic features of the various defects, as these points have been adequately covered by Abbott²⁻⁶ and numerous other investigators.^{12,23,32,37,40}

The prognosis in congenital heart disease appears to depend on the direct effect of the structural defect and the subsequent oxygen unsaturation in the blood.¹⁸ Abnormal shunts of blood through anomalous communications and stenotic orifices constitute a heavy load for the heart and in time may lead to hypertrophy, dilatation, and loss of cardiac reserve.¹¹

In addition, the vulnerability of even slight congenital cardiac defects to bacterial endocarditis is notorious, especially in adolescence and early adult life. Paget,²⁷ in 1844, was among the first to stress the importance of defective or erroneous development in a heart as predisposing to inflammatory disease. This observation was subsequently corroborated by Osler²⁶ in 1886, by Horder¹⁹ in 1909, by Lewis and Grant²⁴ in 1922, and by Abbott and her contemporaries.^{1,9}

The development of bacterial endocarditis or endarteritis on the margins of or adjacent to a congenital cardiac defect comprises one of the most serious hazards to the patient with this disease. The presence of local deformities or tissue changes and the influence of mechanical strain and trauma, as, for example, malformed cusps, deformed valves, patent ductus arteriosus, and interventricular septal defects,^{13,23} give rise to areas of fibrosis and sclerosis which offer sites of lowered resistance for the lodgment and growth of virulent organisms.⁵

Material.—This report is based on a study of necropsied cases with congenital cardiac defects in the following Boston hospitals, during the years indicated: 1, the Peter Bent Brigham Hospital, 1913 to 1940; 2, the Boston City Hospital, 1896 to July 1, 1941; 3, the Massachusetts General Hospital, 1897 to August 1, 1941; and, 4, the Infants' and Childrens' Hospitals, 1915 to 1940. In the protocols reviewed special attention was paid to: 1, sex; 2, age at time of death; 3, type of cardiac defect or defects; 4, evidence of superimposed rheumatic infection; and, 5, the presence of acute or subacute bacterial endocarditis or endarteritis.

All cases were included that had significant cardiac anomalies, whether or not they occurred in combination or alone, or if they were of primary or secondary importance. However, no case was listed if the single defect was either: 1, a patent foramen ovale under 1 year of age, unless it was 1 cm. or more in diameter, and completely or partially undefended to allow true admixture of venous and arterial blood;²⁸ or, 2, a patent ductus arteriosus before the first postnatal month, unless the patency was abnormally wide;³⁶ or, 3, anomalies of the coronary arteries, anomalies of the aorta or its branches, or the pulmonary arteries, or the great veins; or, 4, fenestrations of the semilunar cusps.

In addition, two separate groups of statistics were made, and will be referred to as Group A and Group B, as follows: *A*, all types of significant congenital cardiac defects regardless of age; and, *B*, only cases over 2 years of age and with defects actually vulnerable to the subsequent development of bacterial endocarditis. Thus, in Group B, dextrocardia, congenital rhabdomyomata, hypertrophy, heart block, and the like, were eliminated.

Results. Table 1 shows the collected data on the principal items investigated at each hospital and the corresponding totals.

TABLE 1.—DATA FROM 5 HOSPITALS.

	P.B.B.H.	B.C.H.	M.G.H.	Child H.	Totals.
Total number autopsies	4400	15,638	10,085	3900	34,023
Autopsies C.H.D., Group A*	33	123	82	215	453
Autopsies C.H.D., Group B†	31	74	55	21	181
Autopsy % C.H.D., Group A	0 7	0 8	0 8	5.5	1.3
Autopsy % C.H.D., Group B	0 7	0 5	0 5	0 5	0.5
B.E. directly on C.H.D., A	4	11	9	11	35
B.E. directly on C.H.D., B	4	11	8	7	30
% B.E. in C.H.D., Group A	12 1	8.9	10.9	5.1	6.6
% B.E. in C.H.D., Group B	12 9	14.9	14.5	33.3	16.6
Rheumatic infection in C.H.D.	9	4	10	2	25
B.E. solely on rheumatic site	3	0	1	1	5

Key to abbreviations:

P.B.B.H.—Peter Bent Brigham Hospital, 1913–1940.

B.C.H.—Boston City Hospital, 1896–1941, July 1.

M.G.H.—Massachusetts General Hospital, 1897–1941, Aug. 1.

Child. H.—Infants' and Childrens' Hospitals, 1915–1940.

(all in Boston)

C.H.D.—Congenital cardiac defects.

B.E.—Bacterial endocarditis and endarteritis, acute and subacute.

* Group A, all types of significant congenital cardiac defects, all ages.

† Group B, cardiac defects, only over 2 years of age, and vulnerable to the development of bacterial endocarditis.

Congenital cardiac defects were present in 1.33% of the total autopsy population (453 out of 34,023 cases), but only 0.5% were over 2 years of age (181 cases). The higher incidence in Group A was to be expected, as 60% of this group was under the age of 2 years, for the more serious and more frequent complex lesions are usually fatal early in life.

The incidence of superimposed bacterial endocarditis and endarteritis was 6.6% in Group A (35 of 453 cases) and 16.6% in Group B (30 of 181 cases). Inasmuch as infectious endocarditis occurs but rarely below the age of 2 years, its higher incidence in Group B is obvious. These results are comparable to those reported by previ-

ous investigators (Table 2). The wide range of figures in this table may be accounted for partly by the variability of the criteria used in statistical studies. As pointed out by Roberts, these factors include: 1, the actual meaning of proportion: whether it is the number of cases of congenital heart defects per 1000 autopsies or deaths or admissions; 2, the variation according to the relative size of the age groups serving as a basis for the data: congenital heart disease is much less frequent over 2 years of age; and, 3, the influence of the degree of interest among clinicians and pathologists.³¹

TABLE 2.—INCIDENCE OF BACTERIAL ENDOCARDITIS AMONG CONGENITAL CARDIAC DEFECTS, AS FOUND AT NECROPSY, FROM THE LITERATURE.

Author	Total autopsies.	C.H.D., autopsies.	% C.H.D.	B.E. in C.H.D., autopsies.	% B.E. in C.H.D.
Abbott, M. E. ⁴	3633	43	1.2		
Abbott, M. E. ²	656	..	129	19.6
De La Chapelle ¹⁰	8683	31*	0.4	9*	30.0
Philpott, N. W. ²⁹	7240	80	1.1	5	6.3
Terplan and Sanes ³⁵	336	21†	6.3	1†	4.8
Ash and Harshaw ⁷	1075	34†	3.2	2†	5.9
Rannels and Propst ³⁰	4255	36	0.9	5	13.9
Jacobius and Moore ²⁰	1600	131	8.1	9	6.8

* Major types of congenital cardiac defects only.

† Infants and children over 12 years of age only.

Sex Distribution. There were 245 (54%) males among the total group of 453 cases of significant congenital cardiac defects, and 208 (46%) were females. In Group B, the proportion was 60% males to 40% females, a ratio of 3 to 2. This same distribution of the sexes held true among the 35 patients with superimposed infectious processes. The predominance of the male sex in congenital heart disease both with and without bacterial endocarditis has been borne out by the majority of previous reports (Table 3).

TABLE 3.—SEX DISTRIBUTION IN CASES OF CONGENITAL CARDIAC DEFECTS, FROM THE LITERATURE.

Author	C.H.D. autopsies.	% male.	% female.
Abbott, M. E. ⁴	859	58.4	41.6
Lecch, C. B. ²²	170	61.0	39.0
Terplan and Sanes ³⁵	21*	57.1	42.9
Jacobius and Moore ²⁰	131	48.1	51.9
Rannels and Propst ³⁰	36	61.1	38.9
Gibson and Clifton ¹⁴	105*	59.0	41.0

* Infants and children under 12 years of age only.

Age Distribution. Of the patients, 269 (60%) died before the age of 2; 5 of these had developed bacterial endocarditis. For the remaining 184, no predominance was shown in any one age group; but of the 30 who had superimposed inflammatory processes, 80% died before the age of 40. The average age at death for patients with cardiac anomalies in Group B was 37 years, and for those with complicating infectious endocarditis, it was 22 years in Group A

and 26 years in Group B. The highest incidence of bacterial endocarditis in congenital hearts fell in the second and third decades.

Of the 5 patients under 2 years of age who developed acute bacterial endocarditis, 3 lesions were on the site of a congenital pulmonic stenosis, 1 of which was part of a tetralogy of Fallot, and 2 were on margins of or adjacent to a defect in the interventricular septum. The youngest of the entire group was a 3 week old baby girl, with bacterial endocarditis on an interventricular septal defect. The oldest patient to have a cardiac defect the site of a superimposed infectious process was a 62 year old man with a congenital bicuspid aortic valve.

Rheumatic Infection. At this point, we should like to consider briefly the incidence of rheumatic infection in congenital heart disease. Acquired rheumatic heart disease appears to be fairly common among congenital cardiacs who reach adult life. This apparent predilection has been noted to be true especially of congenital bicuspid aortic valves and of interauricular septal defects.

The incidence of rheumatic infection in hearts with congenital bicuspid aortic valves has been variously reported as between 16% and 44%,^{16,21} and that in hearts with interauricular septal defects as about 13%.³³ Lutembacher²⁵ in 1916 described a defect of the interauricular septum associated with mitral stenosis, a combination that has since been referred to as Lutembacher's syndrome.

In the present series of 181 hearts with congenital defects, 25 (14%) had superimposed rheumatic infection. The nature of the cardiac defect was as follows: congenital bicuspid aortic valve in 8 cases (15% of the 52 instances of this defect); interauricular septal defect in 5, 2 of which were considered true Lutembacher examples; interventricular septal defect, 4-cusped aortic valve, coarctation of the aorta, and accessory septa, in 2 each; and patent ductus arteriosus, bicuspid pulmonic valve, congenital pulmonic stenosis, and tetralogy of Fallot in 1 each.

Subacute bacterial endocarditis was present in 8 of these 25 hearts, and in 5 was solely on the site of the rheumatic lesion.

Significant Types of Congenital Defects. The total number of the most significant types of congenital cardiac defects, as found in all four hospitals investigated, is listed in the order of their frequency, together with the incidence of superimposed infectious processes (Table 4). Several of these defects will now be considered in greater detail.

Interauricular Septal Defects. The most common of all congenital cardiac abnormalities was a defect in the interauricular septum. It was present in 40% of all hearts reviewed and in 25% of those over 2 years of age. In 85% to 90% of the cases, it was associated with other defects. Its relation to rheumatic infection has been indicated above.

Of the 179 times this defect occurred, it was as a persistent ostium

secundum, including a widely patent foramen ovale 1 cm. or more in diameter, in 140 of them; as a persistent ostium primum in 20; as multiple defects in 9; and as the complete absence of the septum in 10. There were no instances of bacterial endocarditis complicating an interauricular septal defect. This was significant considering that 45 were over 2 years of age.

Rokitansky³⁵ in 1875 gave the first complete description of this defect. Excellent recent reviews have been contributed by Roessler³³ in 1934, and by Bedford, Papp and Parkinson⁸ in 1941. In these reports, too, the incidence of superimposed bacterial endocarditis is extremely rare.

TABLE 4.—CONGENITAL HEART DISEASE IN ALL 4 HOSPITALS, WITH INCIDENCE OF BACTERIAL ENDOCARDITIS.

Type of defect.	Group A.			Group B.		
	C.H.D.	B.E.	% B.E.	C.H.D.	B.E.	% B.E.
Interauricular septal defects . . .	179	0	0	45	0	0
Interventricular septal defects . . .	164	17	10.4	31	13	41.9
Patent ductus arteriosus	134	4	3.0	14	4	28.6
Congen. bicuspid aortic valve	63	11	17.4	52	11	21.2
Congen. pulmonic stenosis	43	8	18.6	17	5	29.4
Coarctation of aorta	33	1	3.0	10	1	10.0
Congen. bicuspid pulmonic valve	21	0	0	9	0	0
Congen. pulmonary atresia	15	0	0	2	0	0
Cor triloculare biatriatum	13	1	7.7	2	1	50.0
Congen. aortic stenosis	11	0	0	3	0	0
Congen. tricuspid stenosis	9	0	0	1	0	0
Congen. mitral stenosis	7	0	0	3	0	0
Congen. subaortic stenosis	2	1	50.0	2	1	50.0
Maladie de Roger	44	10	22.7	14	8	57.1
Tetralogy of Fallot	16	2	12.5	7	2	28.6

Interventricular Septal Defects. Next in order of frequency was a defect of the interventricular septum, usually at the base of the heart, immediately posterior to the aortic valve. It was present in 0.48% of all autopsies and in 36% of congenital hearts. One-fifth of the latter cases were over the age of 2 years.

The frequent finding of vegetations on the margins of the defect in the interventricular septum and on the area of endocardial fibrosis at the point of contact of the blood stream on the wall of the right ventricle opposite the septal defect illustrate the importance of foci of mechanical stress.^{4,15}

Acute or subacute bacterial endocarditis was present in 17 (10%) of the total of 164 hearts showing an interventricular septal defect; but in only 6 cases was the infectious process superimposed directly on the site of the defect. In the group of patients over 2 years of age, bacterial endocarditis was present in 13 (42%) of the 31 hearts with this defect, yet in only 5 (16%) was it directly on the septal defect. In the remainder of each group, the underlying site often included the tricuspid valve.

The name of Roger³⁴ is associated with uncomplicated localized interventricular septal defect. The incidence of bacterial endocarditis in Roger's disease was 23% in patients of all ages and 57% in those over 2 years of age.

Patent Ductus Arteriosus. The ductus arteriosus completes its useful functions at birth and normally becomes obliterated by the end of the first postnatal month.³⁶ Although it may remain open as a compensatory bypass for obstruction of the pulmonic or aortic valves, patency of the ductus constitutes an arteriovenous shunt from the descending aorta to the pulmonary artery, and thus diverts blood from the peripheral circulation.

The flow of blood through the patent ductus arteriosus and against the wall of the pulmonary artery opposite to the ductal opening gives rise to local intimal thickening and the formation of atheromatous plaques at these sites.³⁹ These atheromatous areas tend to attract platelet thrombi which in turn become infected by organisms circulating in the blood stream and produce vegetations. In addition to the ductus and the pulmonary artery, infectious processes are very apt to involve the aortic and pulmonic valves. In fact by the time the 4 cases of bacterial endocarditis with patent ductus in the present series were examined postmortem the vegetations in each instance had spread beyond the ductus to other parts of the heart.

There were 134 instances of this defect, an incidence of 0.39% of all autopsies, and of 30% among congenital cardiac defects. Only 14 (10%) of these were over the age of 2 years, 4 (28.6%) of which had bacterial endarteritis or endocarditis. Ten of the 14 cases were uncomplicated. The nature of the complicating defects in the other 4 was: tetralogy of Fallot in 2, bicuspid semilunar valves and coarctation of the aorta in 1 each. The defect was present in patients of every age group and the oldest was 65 years; yet 50% died in the second and third decades. Two of the 10 uncomplicated cases had superimposed infectious processes. Both of these were between 20 and 30 years of age. The susceptibility of patients with patent ductus to bacterial endocarditis and endarteritis may partly explain why the uncomplicated defect is relatively less frequent in older individuals.²³

Recently a more optimistic attitude has prevailed toward the life expectancy of patients with uncomplicated patent ductus arteriosus, since Gross and Hubbard,¹⁷ in 1938, reported the first successful ligation of this defect. The purposes of this operation are threefold: 1, to relieve the cardiac strain and thus to avert future cardiac failure by diminishing the total work of the heart; 2, to prevent retardation of mental and physical development which otherwise may result from decreased output through the aorta; and, 3, to diminish the incidence of superimposed bacterial endarteritis and endocarditis.¹⁷

At the present time, it is generally agreed by workers in this field that one can hardly foretell whether ligation of a patent ductus will actually diminish the incidence of bacterial endarteritis. It appears reasonable to believe, however, that if operation is performed early enough in life before thickened endocardial plaques are formed in the pulmonary artery, the possibilities of future superimposed infectious processes might be thwarted.

Congenital Bicuspid Aortic Valve. The macroscopic criteria used to determine the congenital nature of the bicuspid aortic valve were first clearly defined by Sir William Osler²⁶ in 1886. It was not until 1923 that the classic work of Lewis and Grant microscopically differentiated between the congenital and acquired lesions by noting the distribution of the elastic tissue of the aortic media and its relation to the annulus fibrosus.²⁴

Gross,¹⁶ in 1937, injected an element of doubt into the true antenatal character of uncomplicated bicuspid aortic valve in adults by maintaining that the fused commissural raphé in these cases to be usually the result of acquired disease, frequently rheumatic in type. Koletsky,²¹ in his recent review, however, was not able to confirm Gross' contentions. Koletsky makes use of the original observations of Osler and of Lewis and Grant in pointing out that the differentiation of congenital and acquired fusion still depends on the gross and microscopic character of the congenital ridge and of the acquired commissural raphé. It is obvious that with confusion in pathologic interpretation accurate statistics of incidence cannot be available.

The incidence of congenital bicuspid aortic valve in the general autopsy population was 1.5% in the present series. Among congenital cardiac defects of all ages, it was 13.9% and in Group B, 28.7%. Eighty per cent of the cases with this defect were uncomplicated, all over the age of 2. Of the associated anomalies, coarctation of the aorta and patent ductus arteriosus were the most frequent. The high incidence of uncomplicated lesions in adults may be due to the failure of infants and children with coexisting cardiac abnormalities to survive.

Congenital bicuspid aortic valve is not in itself of serious import, but its clinical significance is greatly increased by its tendency to undergo sclerotic processes and thus provide a nidus for the invasion of infective agents. Bacterial endocarditis was present in 17.4% of all cases of the defect in our series and in 21% of those in Group B. The incidence of this complication in the literature^{21,26} ranges from 6% to 66% with that reported by Lewis and Grant²⁴ as 23%.

Tetralogy of Fallot. In this anomaly (stenosis of the pulmonic valve, interventricular septal defect, dextraposition of the aorta, and hypertrophy of the right ventricle) the cusps of the stenosed pulmonic valve and the margins of the septal defect constitute

potential foci for eventual sclerosis, which in turn is predisposed to infectious processes. The incidence of the tetralogy of Fallot among congenital cardiac defects was 3.8% in Group B. Bacterial endocarditis was present as a complication in 12.5% of all such cases and in 29% of those in Group B.

Congenital pulmonic stenosis, not a part of the tetralogy of Fallot, both with and without a defect in the interventricular septum, was present in 9.5% of all cardiac anomalies. Infectious processes supervened in 19% of all cases of congenital pulmonic stenosis and in 29% of these cases in Group B.

As it is not the purpose of this paper to discuss all the different types of congenital cardiac defects, those anomalies that were not the sites of acute or subacute bacterial endocarditis or endarteritis in sufficient numbers will not be considered in further detail. Suffice it to say that, at the present time, of those congenital heart lesions predisposed to bacterial endocarditis, the most promising from the point of view of prevention or cure are cases of patent ductus arteriosus and possibly interventricular septal defects. It is along these lines that we may expect further outstanding contributions in the near future.

Summary. The protocols of four Boston hospitals were reviewed to determine the incidence of acute and subacute bacterial endocarditis and endarteritis among congenital cardiac defects. Special attention was paid to sex, age at time of death, type of cardiac defect and superimposed rheumatic infection.

In 34,023 autopsies, 453 (1.3%) contained significant congenital cardiac defects, 181 of which (40% of the 453) were in patients over the age of 2 years.

Evidence of bacterial endocarditis was present in 6.5% of the 453 cases and in 16.5% of the 181 cases over 2 years of age.

The distribution of males and females was in a proportion of 3 to 2 in both the total group with cardiac defects and in those who showed infectious endocarditis.

Sixty per cent of the patients died before the age of 2 years. For the rest, no predominance was shown in any one age group. The highest incidence of bacterial endocarditis fell in the second and third decades.

Twenty-five (14%) of the 181 hearts with congenital defects were further complicated by rheumatic infection. Congenital bicuspid aortic valve and interauricular septal defects were the most frequent underlying cardiac anomalies, and subacute bacterial endocarditis was present in 8 of these 25 rheumatic hearts.

The incidence of bacterial endocarditis in the most significant cardiac defects was as follows: interauricular septal defects, none; interventricular septal defects, 42% of all and 57% of the uncomplicated cases over 2 years of age; patent ductus arteriosus, 28.6%

of all and 20% of the uncomplicated cases over 2 years of age; bicuspid valves, 17.4% of all and 21% of those over 2 years of age; tetralogy of Fallot, 12.5% of all and 29% of those over 2 years of age; pulmonic stenosis, 19% of all and 29% of those over 2 years of age.

We would like to express our appreciation to the Pathology Departments of the Boston City Hospital, the Massachusetts General Hospital, and the Infants' and Childrens' Hospitals for permission to review their autopsy records.

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THE ACTION OF FURMETHIDE (FURFURYL-TRIMETHYL-AMMONIUM IODIDE) ON THE CARDIOVASCULAR SYSTEM IN MAN.*

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THE use of Furmethide (furfuryl-trimethyl-ammonium iodide) in the treatment of paralysis of the bladder has recently been studied.¹ Furmethide is closely related chemically to mechohyl, doryl, acetylcholine and muscarine, all of which strongly influence cardiovascular function. It was therefore thought to be essential to study the action of Furmethide on the cardiovascular system, in order to determine the dosages which are safe and comfortable for use in man. Other investigators have reported observations on a small number of patients of the effects on the cardiovascular system of from 1 to 6 mg. administered subcutaneously^{2,3} and from 5 to 20 mg. administered by mouth.³ In the present study, the effects of these and larger doses have been studied more extensively in a larger number of subjects.

Material and Methods. Thirty-two experiments were done on 29 subjects, varying in age from 15 to 55 years; 14 were men. None had cardiovascular, pulmonary or gastro-intestinal disease. All studies were made with the subjects in the semirecumbent position several hours after the last meal; the subjects rested for at least 15 minutes before the start of the experiment. Measurements of blood pressure, pulse and respiratory rates, and in some cases of venous pressure, were then made and repeated until constant. The drug was then given subcutaneously, or orally in the form of tablets; in a few instances Furmethide was dissolved before oral administration to facilitate absorption from the intestinal tract. Of the subjects receiving Furmethide parenterally, 5 received 3 mg.; 6 received 5 mg.; 4 received 7 mg.; 5 received 10 mg.; 1 received 20 mg. Of the subjects receiving the drug orally, 4 received 10 mg.; 5 received 25 mg.; 1 received 35 mg.

When Furmethide was given subcutaneously, the pulse rate and venous and arterial blood pressures were measured every minute, and an electrocardiogram was taken every 5 minutes; observations of respiratory rate and oral temperatures were also made from time to time. When the drug was given orally, pulse rates and arterial blood pressures were measured every 5 to 15 minutes, at which time an electrocardiogram was also taken. Signs and symptoms of side reactions were noted when they occurred.

Observations. Pulse Rate. Tachycardia occurred in all but 2 of the patients receiving the drug parenterally, the maximal rise in

* This investigation was aided by a grant from the Smith, Kline and French Laboratories, Inc.

pulse rate varying between 10 and 40 beats per minute (Figs. 1, 2, 3, 4). The tachycardia began within 2 minutes after the administration of the drug, reached its maximum within 5 minutes, and was maintained to some extent for as long as 60 minutes in some instances, although usually the pulse rate returned to normal in 30 minutes. The amount of rise in pulse rate was somewhat greater with large doses, but not in ratio to the increment of dosage.

No changes in pulse rate occurred during periods of observation as long as 2 hours in patients receiving the drug orally.

Systolic Blood Pressure. A fall of systolic blood pressure was observed in 18 of the 21 patients receiving the drug parenterally (Figs. 1, 2, 3, 4). In these cases the decrease began within 1 to 3 minutes after the administration of the drug, reached its maximum within 5 minutes and disappeared within 5 to 45 minutes; in all instances but 1 in which the fall was more than 15 mm. of mercury, normal levels were reached within 10 minutes. The amount of maximal decrease ranged between 10 and 40 mm.; it was greater than 15 mm. in only 6 of the 18 instances, being more than 20 mm. in only 2. In 12 cases the fall in systolic pressure was followed by a rise above the control level. In 2 cases no fall of systolic pressure occurred, and in 1 case a rise was observed from the very time of injection. Although more marked depression of the blood pressure was usually seen with larger doses of the drug, this was not a constant finding. The only instance in which a rise of systolic pressure without a fall at any time occurred in a patient receiving 10 mg. subcutaneously.

No patients receiving the drug orally showed any change in systolic pressure.

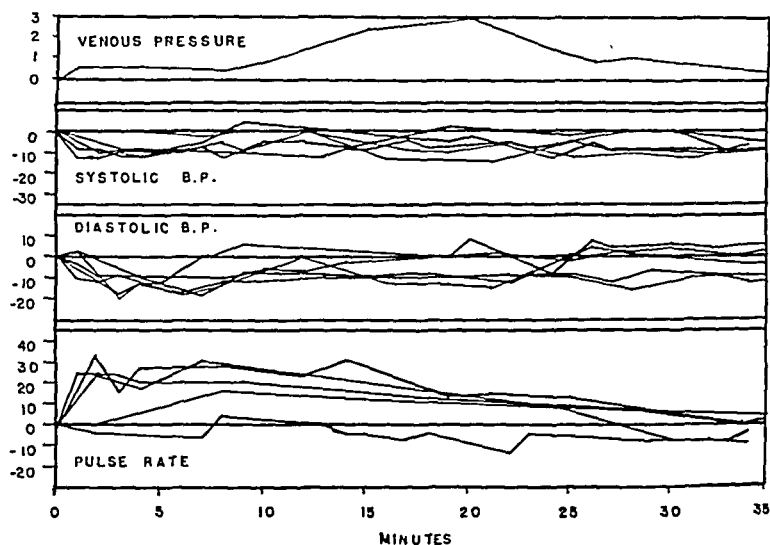
Diastolic Blood Pressure. In patients receiving the drug by injection, a fall of diastolic pressure occurred within the first 3 minutes of the experiment; the maximum fall was noted shortly after the maximal fall of the systolic pressure, and the diastolic pressure returned toward normal at a much slower rate than the systolic, often remaining somewhat depressed up to 45 minutes after the administration of the drug (Figs. 1, 2, 3, 4). The maximal fall in diastolic blood pressure was between 10 and 35 mm.; it was greater than 20 mm. in only 6 instances.

Patients receiving the drug orally showed no change in diastolic blood pressure.

Venous Pressure. The venous pressure was measured in 8 patients receiving the drug by injection (Figs. 1, 2, 3, 4). In all cases a rise of venous pressure was observed 1 to 3 minutes after the administration of the drug. The rise reached a maximum within 5 to 20 minutes and returned to the control level within 40 minutes of the beginning of the experiment. The maximal rise in venous pressure was between 0.5 and 5.5 cm. of water. The variations in venous pressure appeared to be related to the degree of flushing

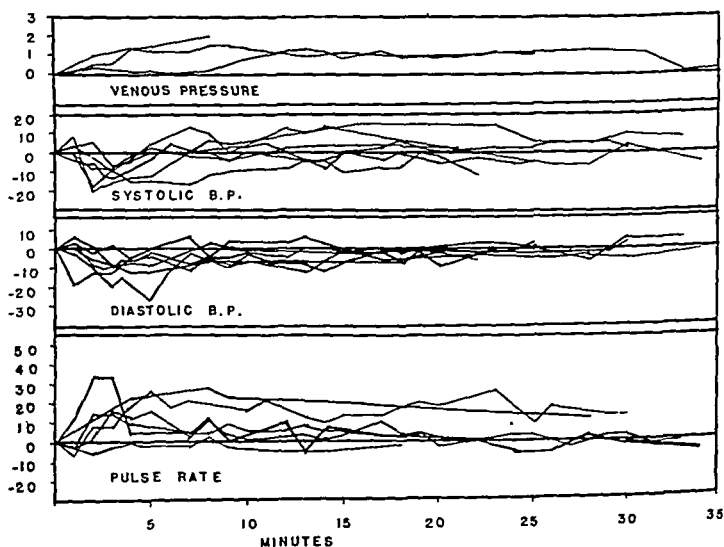
shown by the patient rather than the variations in arterial blood pressure.

Electrocardiograms. In no case were changes in the P-R interval or the form of the T wave noted. Tachycardia was a constant occurrence; however, the P-R interval did not become significantly



3MG FURMETHIDE S.C.

FIG. 1.—The effect of subcutaneous injection of 3 mg. of Furmethide.



5 MG FURMETHIDE S.C.

FIG. 2.—The effect of subcutaneous injection of 5 mg. of Furmethide.

shortened even when the heart rate increased strikingly. Extrasystoles, both ventricular and auricular in origin, were seen in

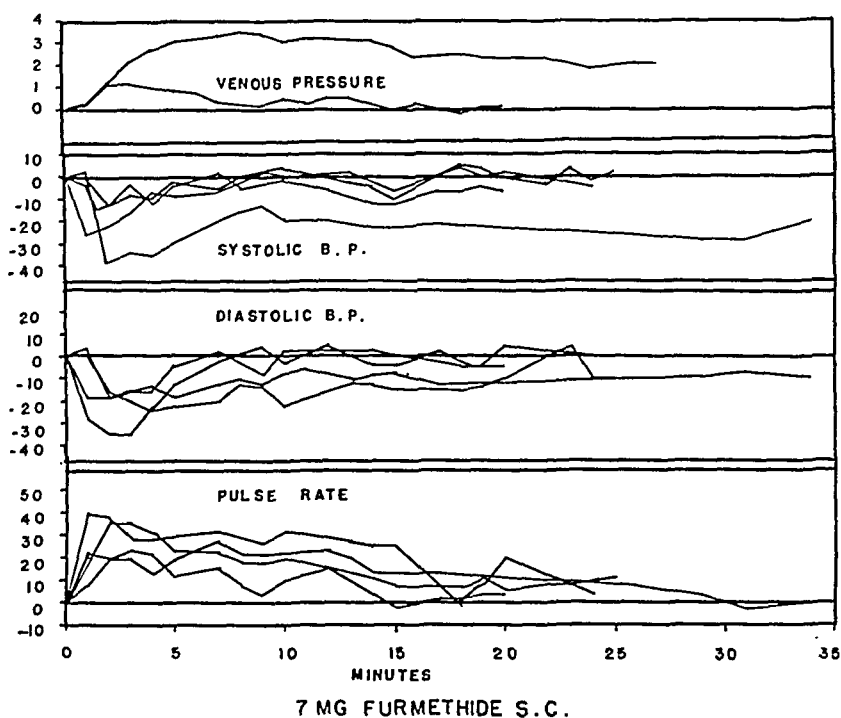


FIG. 3.—The effect of subcutaneous injection of 7 mg. of Furmethide.

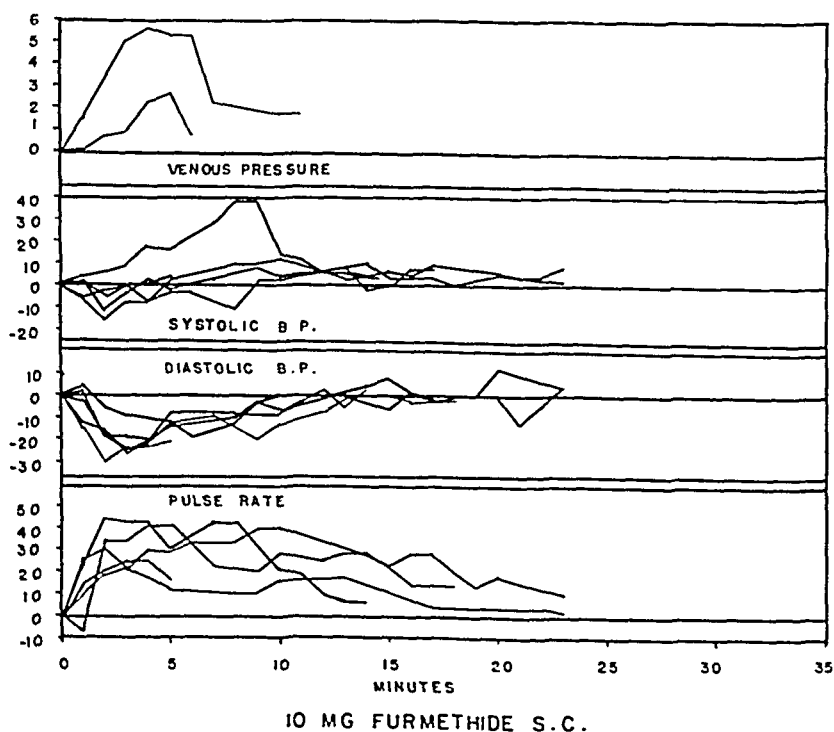


FIG. 4.—The effect of subcutaneous injection of 10 mg. of Furmethide.

several patients. In no case was their incidence during the period of action of the drug higher than during the control period.

Capillaries of the Skin. In patients receiving the drug by injection, flushing and a subjective feeling of warmth were observed 1 to 2 minutes after the beginning of the experiment. The reaction reached a peak at approximately 5 minutes and disappeared within 10 to 30 minutes after injection. As noted above, the onset and severity of the flush were paralleled by changes in venous pressure.

Patients receiving the drug orally failed to show any capillary response during the first hour of observation. In 1 patient receiving 10 mg. dissolved in water after a fast of 18 hours, mild vasodilatation occurred after 1 hour. No other patients receiving 10 mg. orally showed evidence of reactions. Of the patients receiving 25 and 35 mg. orally, all except 1 experienced feelings of mild flushing 2 to 4 hours after taking the drug. These reactions lasted up to 1 hour.

Other Reactions. Bladder. All patients receiving the drug parenterally who had not emptied their bladders shortly before the beginning of the experiment experienced a desire to urinate. In the case of the patient receiving 20 mg. subcutaneously, urgency was experienced when the bladder contained only 35 cc. of urine. None of the patients who received the drug orally experienced any immediate desire to urinate; it was impossible to state whether or not desire to void which occurred later was a result of the action of the drug.

Gastro-intestinal. Two patients receiving 3 mg. of the drug parenterally experienced mild transitory nausea; both were known to be of a neurotic temperament. No other gastro-intestinal symptoms occurred, except in 1 small woman who had mild fleeting lower abdominal cramps and in 1 patient who experienced hunger contractions lasting about 1 minute, both occurring with a dosage of 10 mg. subcutaneously. These reactions occurred within 5 minutes after the administration of the drug.

Respiration. No effects on rate or rhythm of respiration were noted in any patients.

Salivary Glands. Patients receiving the drug parenterally experienced increased salivation within the first 5 minutes of the experiment. The degree of reaction varied with the dose. No effect on salivation was noted in patients receiving the drug orally.

Eyes. Patients receiving large amounts of the drug parenterally complained of lacrimation. Small subcutaneous doses had no visible effect on the activity of the tear glands. Two patients who had received 10 and 20 mg. respectively subcutaneously noticed blurring of distant vision and loss of ability to accommodate. In 1 case the patient found his temporary myopia relieved by minus lenses. This effect lasted up to 2 hours.

Skin. In addition to the flush described above, all patients receiving the drug parenterally exhibited copious sweating during the period of the flush.

Discussion. The work of Fellows and Livingston² showed that Furmethide has a general parasympathomimetic effect in animals, its greatest action being exerted on the bladder and the circulatory system. The threshold dose for increasing bladder tonus in the cat was equal to that producing minimal blood pressure depression. Vomiting and diarrhea occurred only after the administration of very large doses; respiratory depression was a terminal effect of excessive dosage in these animals. In man, on the other hand,³ changes in blood pressure have been variable after the subcutaneous administration of doses of 1 to 6 mg.; tachycardia, however, has been a constant occurrence. In a few instances prolongation of the P-R interval and flattening of the T waves of the electrocardiogram have been described.

The results of the present study demonstrate that the major cardiovascular action of Furmethide is on the fine blood-vessels. The discomfort arising from its use in doses over 7 mg. subcutaneously arises from the intense subjective feeling of heat associated with the action of the drug in producing a dilatation of the vessels of the skin; heat is lost so rapidly from the hyperemic skin that the feeling of intense warmth may be followed by sensations of cold and even shaking chills as the body temperature falls. In doses of 3 to 5 mg. subcutaneously, the feeling of warmth is usually not distressing. This is important, since this lower dosage range is effective for the treatment of atony of the bladder.¹ Even when capillary dilatation is extreme, changes of pulse pressure are not marked. Decreases of arterial blood pressure are transitory and not great. The administration of as much as 35 mg. by mouth produces only slight flushing which is not uncomfortable. Patients receiving Furmethide parenterally should be kept covered and in bed until the flush reaction has worn off, in order to guard against great losses of body heat during the sweating and vasomotor reactions.

The rise of venous pressure which occurred in the present study was associated with the onset of vasodilatation and is probably a consequence of the transmission of arterial pressure through the dilated smaller vessels of the tissues. The tachycardia may be due, at least in part, to activation of the Bainbridge reflex⁴ by the increased venous pressure. The occurrence of the tachycardia appears to contraindicate the use of the drug parenterally in patients with evidences of heart disease. The transitory fall in blood pressure may be hazardous to patients with symptoms of coronary artery insufficiency; accordingly, large doses should not be used in such patients until after it has been shown that the smallest doses have no effect. Whenever possible, the drug should be given orally to patients in whom the possibility of significant cardiac disease exists.

Side reactions other than those already discussed—gastro-intestinal, salivary and ocular—occur only when large doses are given and are not dangerous, although the paralysis of accommodation

may be annoying. Effects on the gastro-intestinal motility are so insignificant that Furfmethide is probably safe to use even in the presence of disease of the gastro-intestinal tract.

Summary and Conclusions. The reactions of 29 patients to the parasympathomimetic drug Furfmethide (furfuryl-trimethyl-ammonium iodide) in parenteral doses of 3 to 20 mg., and in oral doses of 10 to 35 mg., were studied. Particular attention was paid to its effects on the cardiovascular system. Transient falls of systolic and diastolic blood pressures, tachycardia and rises of venous pressure occurred in patients receiving the drug parenterally. No such reactions occurred in patients receiving the drug orally. The side reactions include flush, sweating and urgency of urination. In the doses recommended for the treatment of atonic bladders (*i. e.*, 3 to 5 mg. subcutaneously or 10 to 25 mg. orally) these reactions were not so marked as to make the patient uncomfortable.

The drug may safely be repeated after an hour when given subcutaneously, or after 4 hours when given orally.

Large doses of Furfmethide should not be given parenterally to old patients or patients with known heart disease, as the tachycardia and fall in blood pressure may give rise to myocardial infarction. Very small doses should be used first in such patients, gradually increasing the dose after it has been shown that the smallest doses are without effect. The use of Furfmethide by the oral route appears to be preferable in patients with heart disease.

Patients receiving Furfmethide parenterally should be kept covered and in bed until the flush reaction has worn off, in order to guard against great losses of body heat during the sweating and vasomotor reactions.

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THE MECHANISM OF ARTERIAL HYPERTENSION IN EXPERIMENTAL HYDRONEPHROSIS.*

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THE fundamental relationship between the kidney and some forms of arterial hypertension is now clearly established. Clinical

* Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

evidence^{1,10a,b} continues to accumulate suggesting that hydronephrosis has been an etiologic factor in some cases of chronic hypertension. These conclusions are supported by numerous experimental observations.^{8,9,12} However, attempts to induce protracted hypertensive states by experimental hydronephrosis have in general led only to slight transient elevations in the systemic arterial pressure. In an effort to formulate more concisely the mechanism whereby hydronephrosis produces elevations in blood pressure, we have further investigated this problem.

Methods. Trained dogs were used in all experiments, the period of training being considered complete when the diastolic pressure on 3 successive determinations showed a variation of less than 5 mm. Hg. Blood pressures were recorded from the femoral artery of the unanesthetized dog by means of the Hamilton needle manometer.⁴ Hydronephrosis was produced by (a) partial or complete constriction of the ureter with a Goldblatt clamp, or (b) by cannulation of the ureter to the inferior vena cava or one of its tributaries.^{11b} Operations were performed aseptically under nembutal or ether anesthesia, the latter being employed in order to ensure rapid elimination of the anesthetic agent postoperatively. Frequent blood non-protein nitrogen determinations were made prior to and following surgery. All animals were autopsied soon after death and the experiment discarded if gross hydronephrosis was not present.

For purposes of a more complete analysis, some experiments previously reported⁹ have been incorporated into the present study. Including these, the effects of the following procedures were initially investigated: (a) bilateral hydronephrosis following complete and partial ureteral occlusion; (b) unilateral hydronephrosis; and (c) unilateral hydronephrosis and contralateral nephrectomy. As the problem developed, it was found that attempts to produce chronic hypertension by uncomplicated hydronephrosis were unsuccessful. Accordingly, the effect of combining unilateral hydronephrosis with constriction of the contralateral renal artery was studied. In some of these animals the ischemic kidney was later removed.

Results. The data on all series of experiments are summarized in Tables 1 to 6.

1. *The Effect of Bilateral Hydronephrosis Following Complete Ureteral Occlusion.* Complete bilateral ureteral occlusion resulted in a definite hypertension in 4 and a mild hypertension in 2 dogs (V-24, V-26, V-28, W-13, W-19, W-20, Table 1) out of 7. The blood pressure elevation persisted until death in uremia occurred 2 to 6 days postoperatively.

TABLE 1.—EFFECT ON BLOOD PRESSURE OF COMPLETE OCCLUSION OF BOTH URETERS.

Dog No.:	V-24.		V-26.		V-28.		V-27.		W-13.		W-19.		W-20.	
	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Blood Pressure: Control (before oper.)	140	80	150	75	160	85	140	85	175	80	150	80	115	65
Day (postop.):														
1	150	90	120	90	135	100	175	85	150	90	185	105	125	65
2	165	90	dead		dead		dead		185	105	220	140	120	80
3	175	100							dead		215	135	175	110
4	170	100									dead		dead	
5	140	80												
6	dead													
Cause of death	uremia		pneumonia uremia		pneumonia uremia		pneumonia		uremia		uremia		uremia	

S = systolic blood pressure in mm. Hg.

D = diastolic blood pressure in mm. Hg.

2. *The Effect of Bilateral Hydronephrosis Following Partial Ureteral Occlusion.* Postoperatively the systemic arterial pressure rose in 5 of 7 dogs (W-44, W-49, W-50, W-53, W-78, Table 2). The elevation was maintained for a period of 3 to 80 days, the pressure then

TABLE 2.—EFFECT ON BLOOD PRESSURE OF BILATERAL PARTIAL URETERAL OCCLUSION.

Dog No.:	W-44.		W-47.		W-49.		W-50.		W-51.		W-53.		W-78.	
BLOOD PRESSURE:	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Control (before oper.)	170	100	135	85	155	85	170	85	150	80	170	75	140	75
Day (postop.):														
1	175	120	150	85	165	110	150	100	140	75	145	85	150	85
2	205	140					160	100					175	110
3	190	135	170	95	190	105					175	110	175	90
4	dead						160	100						
5			115	65	170	90	180	120						
6			dead										170	85
7					140	105								
8					150	105	145	90			160	95		
10							160	120			150	95		
											dead			
15							135	85					200	100
							dead							
20					135	65							170	85
30					125	75							175	100
					dead									
50													165	85
70													150	115
80													125	100
													dead	

Cause of death . . . uremia pneumonia pneumonia pneumonia uremia pneumonia uremia

S = systolic blood pressure in mm. Hg.

D = diastolic blood pressure in mm. Hg.

tending to return towards the control level in some (W-49, W-50, W-53). In 1 dog (W-44) the severe hypertension was maintained until death in uremia 4 days following operation. In this instance, it was noted that ureteral occlusion was almost complete. No significant blood pressure changes appeared in the remaining dogs (W-47, W-51, Table 2).

TABLE 3.—EFFECT OF COMPLETE UNILATERAL URETERAL OCCLUSION.

Dog No.:	V-32.		W-16.		W-22.		W-26.		W-32.		W-55.		W-57.		W-65.	
BLOOD PRESSURE:	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Control (before oper.)	150	85	150	85	150	70	140	75	150	85	150	75	165	80	150	75
Day (postop.):																
1	165	95	150	85	150	75	155	75	165	95			160	75		
2	170	105							170	105	155	80			160	75
3	160	100	155	90	160	80			160	100					160	75
4	150	85	150	90			170	65*	150	85						
			dead													
8					145	80	170	90					140	90		
							dead									
12	175	90			125	50			175	90	145	75	225	130		
					dead											
20									145	85			190	100	140	80
30	145	85									150	75	190	105	150	90
	dead										dead				dead	
50									155	90			185	85	150	70
									dead				dead		150	70
100															dead	
150															dead	

Cause of death . . . sacrificed pneumonia unknown pneumonia sacrificed sacrificed peritonitis unknown

* Dog excited.

S = systolic blood pressure in mm. Hg.

D = diastolic blood pressure in mm. Hg.

3. *The Effect of Unilateral Hydronephrosis.* Unilateral hydronephrosis produced a transient elevation in arterial pressure lasting for periods up to 50 days in 3 out of 8 dogs (V-32, W-32, W-57, Table 3). This confirms the observations of Hartwich.⁵

TABLE 4.—EFFECT OF UNILATERAL OCCLUSION AND CONTRALATERAL NEPHRECTOMY.

Dog No.:	W-25.		W-54.		W-79.		X-45.		Y-36.	
	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Blood Pressure: (before oper.)	130	75	150	75	170	80	155	80	155	80
Day after operation	L.U.C.		L.U.C.		L.U.C.		L.N.		L.N.	
1	120	70	170	80	155	75			150	90
2							185	100		
3					175	100	175	90		
4	145	80	195	105						
6							150	90		
8									135	80
15									135	70
21					140	70				
31			175	85						
45					185	100				
71			175	105						
79					140	75				
99					175	90				
137					175	90				
145			180	85						
163			210	120						
175			175	90						
	R.N.		R.N.		R.N.		R.U.C.		R.U.C.	
1			200	90	185	90	150	95		
2	140	80					175	100	190	120
3					195	95	180	105	200	120
4	125	75	150	75			200	120*		
	dead						dead		dead	
5										
6					215	125*				
					dead					
7			210	100						
			dead							
Cause of death	sacrificed uremia		uremia pneumonia		uremia		uremia		sacrificed	

* Agonal.
S = systolic blood pressure in mm. Hg.
D = diastolic blood pressure in mm. Hg.
L = left.
R = right.
N = nephrectomy.
U.C. = ureteral occlusion.

4. *The Effect of Unilateral Hydronephrosis and Contralateral Nephrectomy.* In 3 dogs the contralateral normal kidney was removed after the ureteral occlusion and in 2 dogs the nephrectomy was done prior to the unilateral ureteral occlusion (Table 4). The time sequence of nephrectomy to ureteral occlusion had no apparent determining effect on the subsequent blood pressure changes. In 3 of these animals (W-79, X-45, Y-36, Table 4) hypertension developed when a single hydronephrotic kidney remained (Fig. 1). This elevation in blood pressure persisted until death in uremia 4 to 6 days postoperatively; the onset, intensity and duration of the

blood pressure change was similar to that following complete bilateral ureteral occlusion (Table 1). One animal (W-54, Table 4) developed a fluctuating hypertension following unilateral hydronephrosis, but showed no further blood pressure changes following nephrectomy. The remaining dog (W-25, Table 4) showed no blood pressure variations although excretory insufficiency followed removal of the normal kidney.

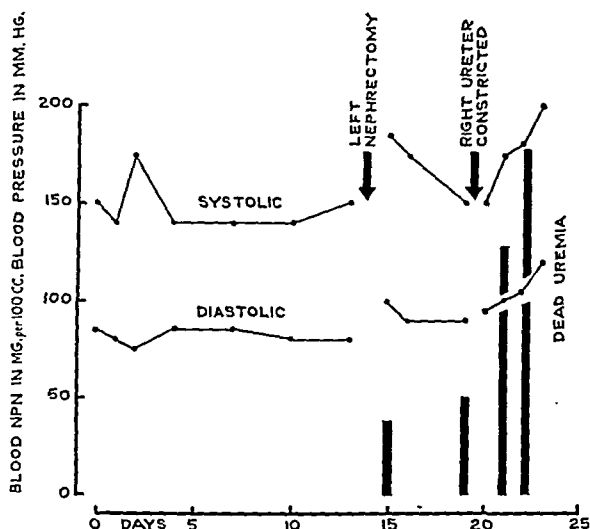


FIG. 1 (X-45).

5. *The Effect of Unilateral Renal Ischemia* and Contralateral Hydronephrosis.* Unilateral renal ischemia was produced in 8 dogs by the method of Goldblatt³ after which the arterial pressure was determined frequently until it remained relatively stabilized at the preoperative control, or at a higher level. In 6 dogs (U-81, U-89, U-99, V-2, V-66, W-86, Table 5) the addition of contralateral hydronephrosis was followed by an elevation in blood pressure lasting for periods of from 3 to 9 days (Fig. 2). The remaining 2 dogs (V-46, X-100, Table 5) showed no significant blood pressure variation following this procedure. These blood pressure changes appeared within 24 hours following ureteral obstruction and persisted at the new levels with but minor fluctuations until the animals died or were sacrificed. In 4 of the dogs (U-81, U-89, V-2, W-86) the elevation in arterial pressure was accompanied by a progressive rise in the blood NPN, the animals dying or were sacrificed in uremia within 5 days following contralateral hydronephrosis.

* By the term renal ischemia, we imply those changes which occur in the kidney following constriction of the renal artery with a Goldblatt clamp, be it actual ischemic, diminished pulse pressure, changes in pulsatile flow or other factors

TABLE 5.—EFFECT ON BLOOD PRESSURE OF CONTRALATERAL URETERAL OCCLUSION FOLLOWING UNILATERAL RENAL ARTERY CONSTRICTION.

Dog No.:	U-81.		U-89.		U-99.		V-2.		V-46.		V-66.		W-86.		X-100.	
BLOOD PRESSURE:	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Control (before oper.)	150	75	155	85	160	75	150	75	165	75	150	75	150	85	120	65
<i>Unilateral Renal Artery Constriction.</i>																
Level after operation .	200	105	175	80	185	85	150	75	150	80	155	70	150	90	125	60
<i>Contralateral Ureteral Occlusion.</i>																
Day after 2d oper.:																
1	225	110	215	125	215	100	175	110	155	75	175	90	175	105	145	90
2	250	135	200	100			200	125					165	95		
3	215	125	225	130	225	105	160	100	150	75	175	95				
4	250	135	225	115	225	105	160	100			†		215	115		
5	225	120*	dead				dead				180	80				
6	220	120			215	115			170	70	dead					
7	220	115			240	120			dead							
8	240	140													125	75
9	dead				235	115										
10					dead											
19															130	65
27															100	75
41															dead	
Cause of death	uremia		sacrificed		sacrificed		uremia		sacrificed		sacrificed		uremia		uremia	

* Hydronephrotic kidney removed earlier in day.

† Ischemic kidney removed.

S = systolic blood pressure in mm. Hg.

D = diastolic blood pressure in mm. Hg.

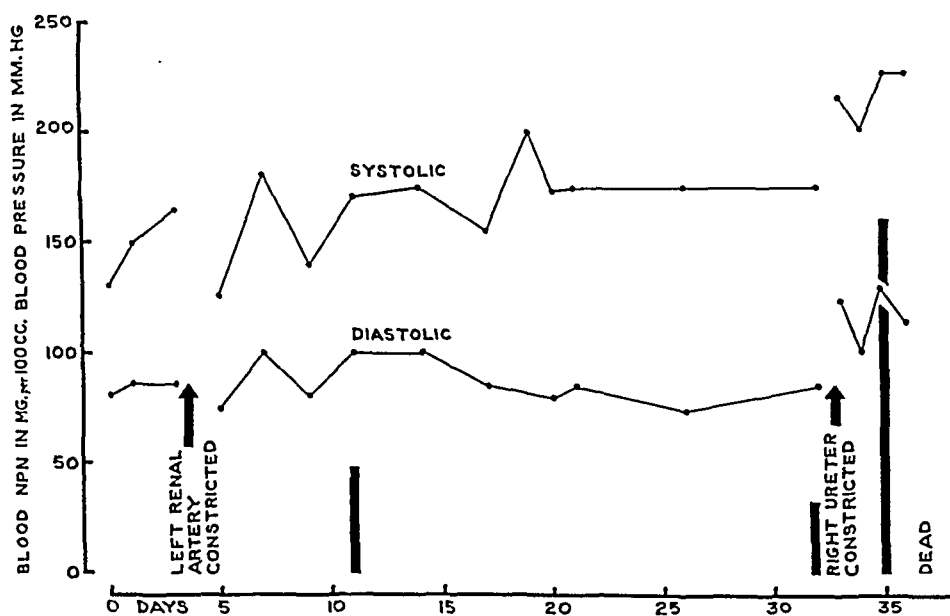


FIG. 2 (U-80).

These results differ strikingly from those observed when the main renal artery of the contralateral kidney was not constricted (Table 3). In the latter instances, none of the dogs died in renal excretory insufficiency.

6. *The Effect of Removal of the Ischemic Kidney in Dogs With Unilateral Renal Ischemia and Contralateral Hydronephrosis.* Nine

TABLE 6.—EFFECT ON BLOOD PRESSURE OF REMOVAL OF ISCHEMIC KIDNEY IN DOGS WITH UNILATERAL RENAL ISCHEMIA AND CONTRALATERAL HYDRONEPHROSIS.

Dog No.:	U-90.		U-94.		V-38.		V-58.		V-93.		W-58.		W-69.		N-59.		N-99.		Y-43.	
	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Control:																				
Before operation	160	80	145	80	160	95	100	75	150	75	160	85	155	80	160	80	175	80	165	85
<i>Unilateral Renal Artery Constriction.</i>																				
After operation	175	115	170	110	225	125	175	125	175	90	175	100	160	80	185	100	175	85	150	95
<i>Partial Contralateral Ureteral Occlusion.</i>																				
After operation	220	130	235	135	*	190	125	220	115	190	95	175	85	225	125	155	110	175	90	
<i>Removal of Kidney With Arterial Constriction.</i>																				
Day after 3d oper.:																				
1	160	90	150	100	110	65	150	80	140	60	215	135	165	80	160	105	160	100	200	120
2	150	100	175	100	210	100	dead	dead	185	85	210	110	165	85	215	125	200	100	200	100
3	dead	dead	dead	dead	210	100	210	100	190	100	200	115	155	70	205	130	200	85		
4					225	115			195	105	205	90			150	90				
5					140	100			dead	dead	dead	dead	dead	dead					170	85
6																			140	80
9																			dead	
14																			155	95
15																			150	100
20																			dead	
25																			uremia	uremia
Cause of death	unknown	unknown	uremia	uremia	uremia	sacrificed	uremia	uremia	uremia	uremia	uremia	uremia	sacrificed	uremia	sacrificed	uremia	uremia	uremia	uremia	uremia

* Contralateral ureteral occlusion and removal of ischemic kidney done at one operation.

S = systolic blood pressure in mm. Hg.

D = diastolic blood pressure in mm. Hg.

dogs with unilateral renal artery occlusion and contralateral hydronephrosis were observed for periods of 1 to 150 days prior to the removal of the ischemic kidney (Table 6). In 1 (V-38) the nephrectomy was done at the same operation as the contralateral ureteral occlusion. In 5 of these 9 dogs (U-90, U-94, V-93, X-59, X-90, Table 6) the addition of the hydronephrosis produced an elevation of the blood pressure; in 1 (X-90) the elevation was from a normotensive level, in the others it was an aggravation of a preëxisting hypertension. This compares with the experience in the preceding series (Table 5) in which the rise was from a normotensive level in 5 out of 6 (U-89, U-99, V-2, V-66, W-86, Table 5) and from a hypertensive level in 1 (U-81, Table 5). We were able to produce a chronic sustained elevation of arterial pressure in 3 dogs (V-93, W-58, X-90, Table 6) lasting for periods of 95, 107 and 84 days respectively prior to nephrectomy (Fig. 3).

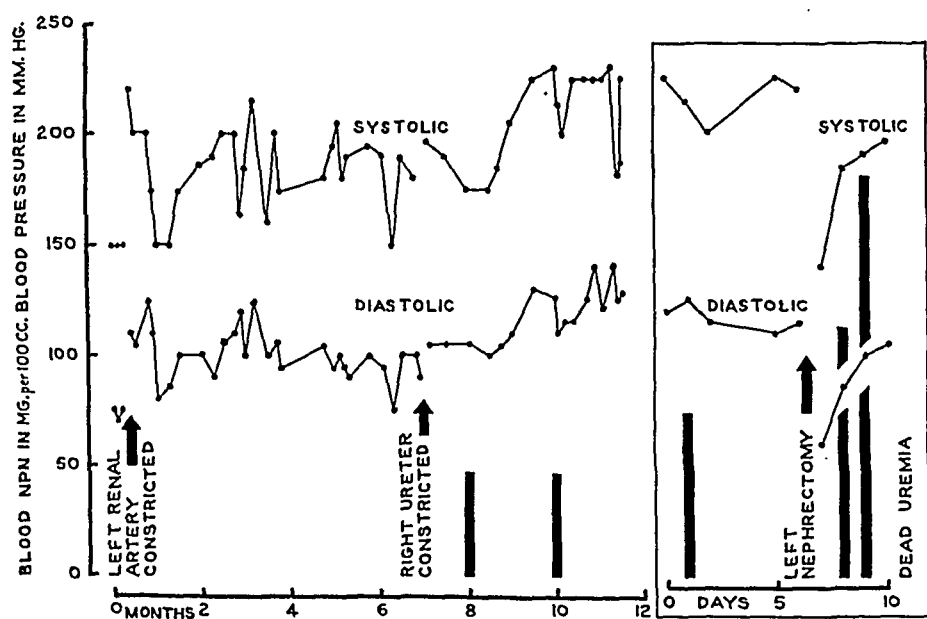


FIG. 3 (V-93).

In the series shown in Table 6, an elevation in the blood non-protein nitrogen occurred in all 5 of the animals showing elevation of blood pressure following the contralateral hydronephrosis, and this was true also in the series of Table 5 showing a blood pressure rise under similar circumstances.

In 7 animals (U90, U-94, V-38, V-93, W-58, X-59, X-90, Table 6) nephrectomy was followed by a persistence (Fig. 3) or increase in intensity of the hypertension.

In the other 2 animals (W-69 and Y-43, Table 6) removal of the Goldblatt kidney was without effect since no hypertension developed.

Discussion. Transient hypertension followed partial ureteral constriction, and a marked hypertension lasting up to 5 days was induced by severe bilateral hydronephrosis or by hydronephrosis in uninephrectomized dogs. Death in uremia terminated the latter experiments. In 3 animals a protracted elevation of the arterial blood pressure unaccompanied by azotemia was induced by adding, at a later date, unilateral hydronephrosis to contralateral renal artery constriction. Persistent systemic arterial hypertension did not occur with uncomplicated hydronephrosis.

Removal of the contralateral ischemic kidney after hydronephrosis had been induced led to a sharp fall in blood pressure toward the normal level.^{11b} This was followed, however, by a gradual increase in blood pressure in 7 out of 10 experiments due to the hypertensive action of the hydronephrotic kidney. Hypertension, in these instances, persisted in most of the animals until death in uremia, which occurred from 3 to 25 days afterwards.

The 3 occasions in this series in which renal failure was present without hypertension offer additional support to the thesis that the excretory and hypertension-producing mechanisms of the kidney are unrelated.^{11b}

Renal hypertension appears to depend upon the ratio of ischemic to normal kidney tissue.^{6,11a} In hydronephrosis both of these factors are affected. The initiating process is a rise in ureteral and intratubular pressure which decreases renal blood flow^{2,8} and therefore may produce true renal ischemia. Of course, the other modifications in renal blood flow which occur in renal artery ligation are also produced to some extent in hydronephrosis. The amount of renal ischemia varies with the duration and intensity of the decreased blood flow. The increased intratubular pressure also results in a certain amount of hydronephrotic atrophy of the normal renal parenchyma. The magnitude and course of the resulting hypertension depends upon these two factors as well as the compensatory increase in normal renal tissue in the opposite kidney. This phenomenon of contralateral compensatory renal hypertrophy explains the occurrence of transitory hypertension in unilateral hydronephrosis. Thus, two fundamental processes advance simultaneously in the same kidney to increase the amount of ischemic and to decrease the amount of normal renal substance. Just as in renal arterial constriction, so it is possible that in hydronephrosis, renal excretory insufficiency may develop without the occurrence of hypertension if the decrease in normal parenchyma is inordinately greater than the amount of ischemic renal tissue. In such an event the process leads primarily to destruction of normal kidney tissue, and this may become great enough to simulate complete nephrectomy.

In those experiments in which ureterovenous anastomosis was used to produce hydronephrosis the possibility exists that the reentry of pressor substances, such as have been extracted from the urine,⁷

may have been responsible for the hypertension that developed. However, this is unlikely since in 2 dogs in this series in which the anastomosis was subsequently interrupted and the urine allowed to drain to the exterior of the body, the induced blood pressure changes remained.

The transitory azotemia accompanying unilateral hydronephrosis indicates that with time the opposite kidney increases its activity to overcome the renal excretory insufficiency. A similar and more persistent renal excretory insufficiency developed, in this investigation, in 13 out of 18 dogs with unilateral hydronephrosis and contralateral restricted renal blood supply. The long persistence of renal excretory insufficiency in these animals may indicate that the kidney with a restricted blood supply may not be able to increase its mass and so cannot compensate for the decrease in renal excretory function. This kidney has lost its capacity for hypertrophy and hence its "reserve" has been diminished. It would seem, therefore, that constriction of the renal artery produces a type of renal excretory insufficiency which is "subclinical" and which cannot be demonstrated by our present methods of analyzing renal excretory function. The addition of hydronephrosis on the opposite kidney is required to make this latent insufficiency manifest.

Summary. 1. Complete unilateral ureteral occlusion in uninephrectomized dogs and complete bilateral ureteral occlusion are followed by a rise in the systemic arterial blood pressure which persists until the animals die in uremia.

2. Partial bilateral and complete or partial unilateral ureteral occlusion are followed by a transient elevation of the arterial blood pressure.

3. The addition of unilateral hydronephrosis to contralateral renal ischemia intensifies any tendency to hypertension. This indicates that the hydronephrotic kidney is actively concerned in the genesis and maintenance of arterial hypertension.

4. Evidence is presented that this mechanism is twofold, in that ischemia and destruction of normal renal tissue probably proceed simultaneously in the same kidney, the initiating factor being a rise in ureteral and intratubular pressure.

5. An explanation is offered for the occasional occurrence of normotension and renal excretory insufficiency observed in hydronephrosis.

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EFFECT OF PREGNANCY ON EXPERIMENTAL RENAL HYPERTENSION IN RATS.*

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IN the course of other experiments on renal hypertension in rats, we observed that 2 animals who were pregnant when their left renal arteries were constricted did not develop high blood pressure and died before delivery with diffuse internal hemorrhages. Although the constriction of one renal artery in normal rats does not necessarily cause a rise in blood pressure, we became interested in studying the possible influence of pregnancy on experimental renal hypertension. We were further stimulated by the contradictory results found in the literature. Some investigators reported that hypertension improves during pregnancy, while others claim that the symptoms become more severe and death follows rapidly.

Goldblatt, Kahn and Hanzal⁹ reported that "most of the hypertensive dogs that have become pregnant have shown a slight or moderate fall of pressure" and that pregnant animals can frequently stand a degree of constriction of the renal arteries which would kill a non-pregnant animal. They suggested that this might be a compensatory effect of the normal kidneys of the foeti.

Dawson, Cressmann and Blalock³ found that constriction of renal arteries in pregnant dogs causes a high incidence of abortion or resorption of the foeti, with elevation in blood pressure ranging from moderate to severe. The blood pressure declines somewhat at the time of delivery and then rises subsequently.

Dill and Erickson⁴ found that bilateral constriction of the renal artery has a deleterious effect on pregnant dogs and rabbits. They

* Funds for this work were made available through a grant to the Department of Neurosurgery, University of Michigan, by the Aaron Mendelson Memorial Trust Fund.

describe an eclampsia-like syndrome accompanied by hypertension, albuminuria, uremia, coma, convulsions, and death. Later Dill, Isenhour and Cadden⁶ repeated the experiments constricting the aorta above the origin of the renal arteries with a measured clamp. Most of the pregnant animals developed an eclampsia-like syndrome similar to the one obtained previously, but only those with moderate constriction developed hypertension. In a recent paper, Dill, Isenhour, Cadden and Kuder⁷ found that pregnancy has no definite effect on the blood pressure of hypertensive rabbits and state that they cannot explain why "reducing the renal blood flow in the pregnant animal produces a fatal vasospastic syndrome while pregnancy in the animal with reduced renal blood flow produces little, if any, effect." One may note that since the renal ischemia was produced in all animals by constriction of the aorta, the blood supply to the uterus was also reduced. A pregnant uterus developing in a hypertensive organism may adapt itself to the existing conditions by developing a large collateral circulation, but the sudden reduction of blood supply to an already pregnant uterus may not be promptly compensated.

Recent experiments of Ogden, Hildebrand and Page¹² suggest that ischemia of the pregnant uterus may play a rôle in the production of experimental hypertension due to constriction of the aorta.

The investigators mentioned above constricted the aorta or both renal arteries. We tried to avoid interference from ischemic uteri or renal insufficiency by constricting only the left renal artery. While our work was in progress Page, Patton and Ogden¹⁴ published a paper in which they show that the blood pressure of hypertensive rats and rabbits with unilateral and bilateral renal ischemia drops during pregnancy and pseudopregnancy, and that the onset of hypertension in pregnant rats is delayed until after parturition.

Method. Eighty-two young adult albino rats were used in our experiments. They were fed dry dog chow, water *ad libitum*, and a daily supplement of fresh lettuce and carrots. The systolic blood pressure was measured using the plethysmographic method described by Byrom and Wilson,² which we modified as follows: The animals were placed in an adjustable container similar to the one described by Williams, Harrison and Grollman.¹⁷ At first, we used animals anesthetized with ether, and later, unanesthetized rats. After a few determinations the animal becomes trained and remains quiet long enough to determine the blood pressure without anesthesia or heat. Instead of soft soap, we sealed the tail into the plethysmograph with a mixture of vaseline and paraffin of a similar consistency. At least three readings were averaged for each blood pressure determination. Hypertension was produced by clamping one renal artery, adapting to the rat the method used by Pickering and Prinzmetal in the rabbit.¹⁵ Care was taken to avoid complete occlusion of the artery, but no effort was made to graduate the degree of constriction, since the exudates which form around the clamp make any such attempt futile.

Rats differ from other animals in that unilateral constriction of the renal artery causes a permanent rise in blood pressure or one lasting several months,¹⁵ long enough for our purpose. This operation is followed by a

relatively high mortality, which under certain conditions is further increased by pregnancy.^{4,6} We therefore waited at least 2 weeks after applying the clamp before mating the rats. Those rats who survived that period of selection had sufficient constriction of their renal artery to produce hypertension without severe renal insufficiency and thus enabled us to study the influence of pregnancy on uncomplicated renal hypertension.

EFFECT OF PREGNANCY ON THE BLOOD PRESSURE OF 6 NORMAL RATS

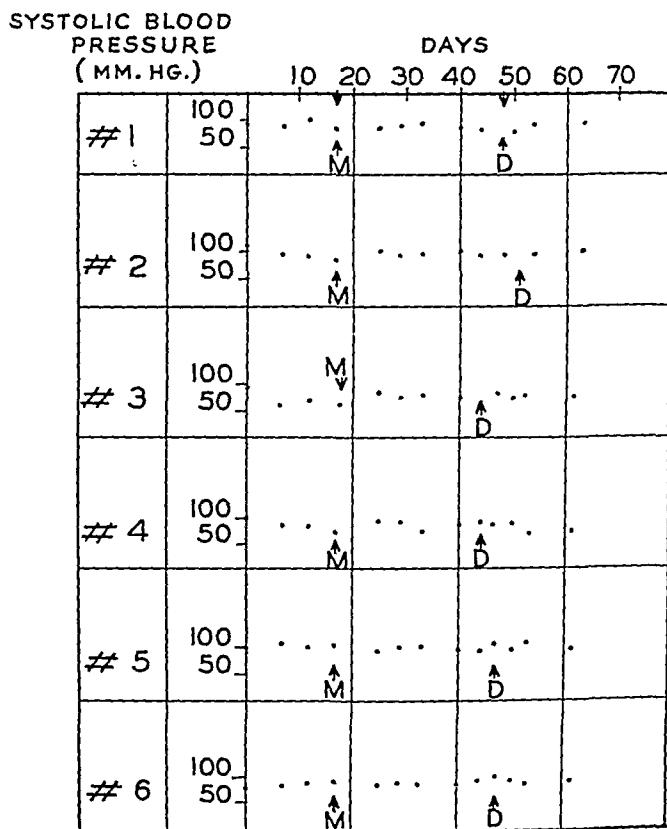


FIG. 1.—Rat Group I. *M* indicates mating; *D* indicates delivery.

Of the 82 rats used in this study, 45 were used solely to determine the normal blood pressure of rats, 6 were used as controls (Group I), and in 31 rats the left renal artery was clamped. Of these, 9 were discarded immediately because of operative mortality or because they did not become hypertensive. Twenty-two became hypertensive; of these, 7 died within 2 weeks and were not considered in this paper, 3 were operated upon while pregnant (Group II) and 12 became pregnant after the operation (Group III).

Results. 1. *Normal Blood Pressure in the Rat.* One hundred and ninety-eight determinations were made on 49 normal rats under ether anesthesia. The blood pressure averaged 84 mm. Hg (60 to 114). Six hundred and fifty determinations were made on 33 nor-

mal unanesthetized rats. The blood pressure averaged 85 mm. Hg (60 to 130).

EFFECT OF PREGNANCY ON THE BLOOD
PRESSURE OF RATS WITH RENAL HYPERTENSION

SYSTOLIC BLOOD
PRESSURE
(MM. HG.)

DAYS

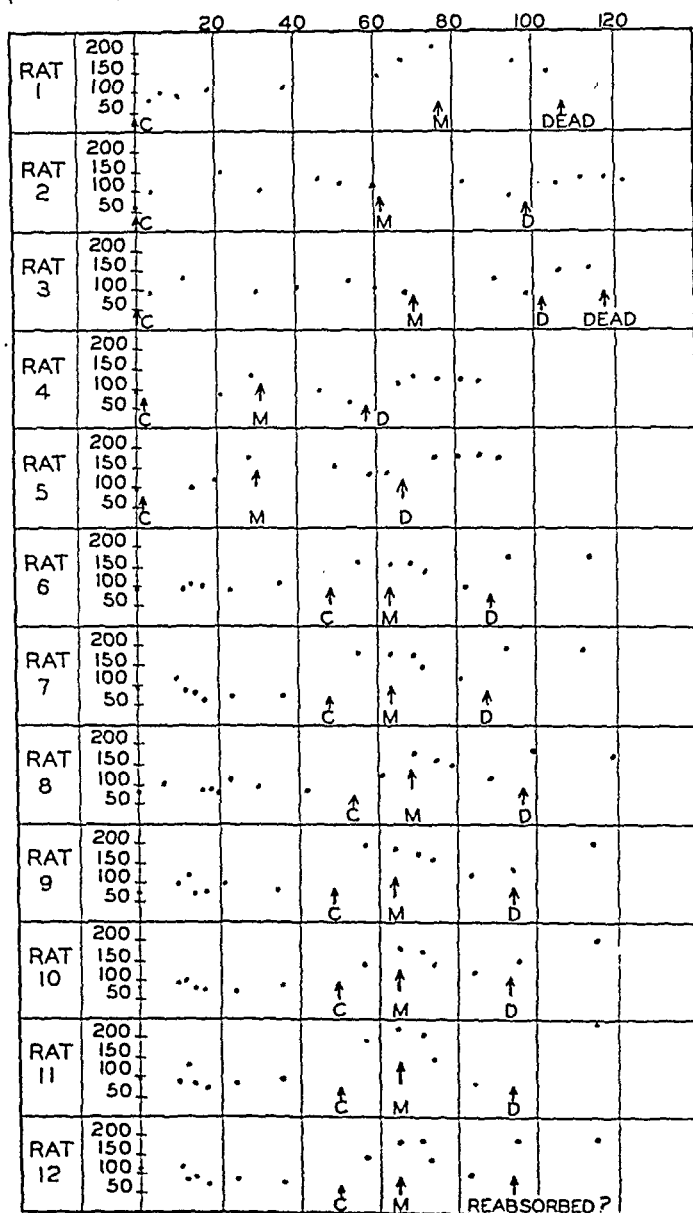


FIG. 2.—Rat Group III. C indicates constriction of the left renal artery; M and D as in Figure 1.

2. *Effect of Pregnancy on the Blood Pressure of the Normal Rat.* (Group I, Fig. 1.) After recording the blood pressure for 17 days, the rats were mated and frequent determinations of blood pressure

were made during pregnancy and for 15 days after delivery. There was no significant change in blood pressure during and after pregnancy.

3. *Effect of Constriction of the Renal Artery in Pregnant Rats.* (Group II.) Only 3 rats were included in this group. The blood pressure of the first rose from an average of 82 mm. Hg before constriction of the renal artery to 92 mm. after 3 days and 114 mm. after 11 days; the twelfth day the animal died. The second rat also died 12 days after its renal artery was constricted. Its blood pressure had dropped from 92 to 60 mm. Hg. The third animal died after 14 days. Its blood pressure had dropped from 76 to 50 mm. Hg. All the animals had diffuse hemorrhages and infarction of the clamped kidney.

4. *Effect of Pregnancy on Preëxisting Hypertension.* (Group III, Fig. 2.) Twelve rats were used in this group. All but 1 survived pregnancy and all of these, except 1, delivered normal foeti. The litters were small; only 1 rat delivered 5 foeti, the others delivered from 1 to 4. In all rats, with no exception, the blood pressure gradually dropped during pregnancy from an average maximum of 174 to an average minimum of 103 mm. Hg beginning towards the end of the first week. The drop was marked in every case; frequently the blood pressure reached normal preoperative levels. After delivery the blood pressure again rose to an average level of 180 mm. Hg, which is higher than the average value before pregnancy, and remained elevated as long as the rats were observed. All of the animals except Nos. 1 and 3 were kept under observation for at least 20 days after delivery.

Discussion. The systolic blood pressure of normal rats averaged 85 mm. Hg (60 to 130) with no significant difference between males and females. Bonsmann¹ by means of a photoelectric method obtained similar results. These values were lower than those obtained by other investigators,^{2,8,17} possibly because most of our experiments were performed in the summer. The average blood pressure of a group of rats during June to September, 1940, was 81 mm.; that of another group of rats during December to February, 1941, was 92 mm. Hg. Hamilton and associates¹⁰ suggested that the blood pressure of street dogs may be reduced during the hot season.

Normal pregnancy had no significant effect on the blood pressure in our experiments. This is in accordance with the results of many investigators, although several others found that pregnancy produces a rise in blood pressure and others found that it produces a drop. (The literature on the subject has been reviewed by Jensen.¹¹)

In 3 rats the left renal artery was constricted during pregnancy. All 3 died in a very short time, 1 had a rise in blood pressure. A similarly high mortality was obtained by Dawson *et al.*³ in analogous conditions in dogs, and by Dill *et al.*⁴ when constricting the aorta above the origin of the renal arteries in rats. In our experi-

ments, since there was no interference with the uterine circulation, death was probably due to renal insufficiency. On the other hand, when pregnancy occurs in hypertensive rats who have survived constriction of the renal artery for a period of time sufficient to permit selection, the blood pressure invariably drops, frequently to normal, and rises again after delivery. We can conclude that pregnancy produces a drop in blood pressure when renal ischemia is sufficient to produce hypertension, but not so severe as to produce damage to kidney function. An eclampsia-like syndrome with hypertension occurs only when the constriction of the renal arteries has been too severe, when the constriction interferes with uterine circulation, or when the clamp is applied during pregnancy and no gradual adaptation is possible.

Three explanations for the drop in blood pressure are possible: 1. Enlargement of the vascular bed due to the development of the uterine circulation. This does not seem very likely, since the drop in blood pressure frequently begins during the first third of the pregnancy, when the uterine circulation is not well developed. Furthermore the arterioles of the uterus, as all other arterioles, are probably subject to the constricting action of the hypertensive agent.

2. Antipressor action of the normal fetal kidneys. This explanation does not seem likely, since the kidneys of the foeti are not yet fully developed when the blood pressure begins to drop; however, here the situation may be analogous to the one in diabetes mellitus, which, according to some authors, improves as the fetal pancreas begins to function.

3. Endocrine mechanism. This mechanism should be more fully investigated. Reynolds and Foster¹⁶ have recently shown that a relation may exist between sex hormones and peripheral circulation, although according to Dill and Isenhour,⁵ the injection of sex hormones into hypertensive rabbits has no effect on blood pressure. Page and Sweet¹³ have shown that although hypophysectomy does not prevent the rise in blood pressure due to constriction of the renal artery, the rise tends to be transient.

Summary and Conclusions. 1. The normal systolic blood pressure of the young adult albino rat was found to average 85 mm. Hg (60 to 130). It is slightly lower during the summer.

2. Ether anesthesia has no appreciable effect on the systolic blood pressure of normal rats.

3. Systolic blood pressure in rats does not change significantly during normal pregnancy.

4. Hypertension of several months' duration can be produced in rats by constricting one renal artery without damage to the general health of the animal.

5. The systolic blood pressure of rats with hypertension due to constriction of one renal artery is sharply reduced during pregnancy, from an average maximum of 174 to an average minimum of 103 mm. Hg.

6. After delivery the systolic blood pressure again rises to hypertensive levels, reaching an average of 180 mm. Hg.

7. Constriction of the renal artery of pregnant rats is followed by rapid decline and death. Hypertension may or may not occur.

8. The influence of pregnancy on experimental renal hypertension in rats is discussed. It is suggested that the drop in blood pressure might be due to an endocrine mechanism.

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QUANTITATIVE UROBILINOGEN EXCRETION FOLLOWING TRANSFUSIONS OF STORED AND FRESH BLOOD.

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THE use of "stored" blood has become more widespread since the institution of "blood banks" in most hospitals. It finds its

* Aided by grants from the Lucius N. Littauer Foundation and Mr. Sidney Spiegel, Jr., for the study of blood diseases.

justification in its ready availability and in the practical and economic advantages resulting to both patient and hospital. Consequently fresh blood transfusions are being given less frequently. There is however some difference of opinion as to the value of stored *versus* fresh blood. Thus Riddell⁹ in his monograph claims that there is a real need for hospitals to store blood as long as it is strictly limited to emergency use. The impression still persists that the changes in blood stored for any length of time militate against its use in many conditions, particularly anemias, infections, sepsis, hemorrhagic diseases, hemolytic anemias and liver diseases. In surgical conditions it is well established that stored blood is of the utmost value in the treatment of shock and hemorrhage. In these states the problem is not so much a hematologic one, but rather a hemodynamic and physico-chemical one.

Stored blood has several disadvantages over fresh blood and these are proportional to the duration of storage. It is known that the leukocytes are rapidly destroyed and that the platelets undergo similar destruction. Chemical changes also occur such as alterations in the glucose, lactic acid and potassium content of the blood.¹⁰ However, the significance of these changes is for the present at least purely academic. There is available a large clinical experience which proves the general therapeutic value of stored blood, and thereby lessens the importance of the above-mentioned changes. This impression is further borne out by the apparent less frequent incidence of transfusion reactions following the use of stored blood.

The major question is the fate of the red blood cells. Although there is a destruction of a small part of the red blood cells in storage and the erythrocyte fragility increases progressively with the duration of storage, these changes do not militate against the use of this type of blood in general medical conditions. Previous work by us¹⁰ and others^{5,16} has shown that blood stored over 10 days usually causes a transient jaundice due to the initial destruction of the older cells transfused. A knowledge of the fate of the younger cells is however of utmost importance in the treatment of the anemias since the therapeutic result is directly dependent upon the viability of the transfused red blood cells. Numerous methods for the detection of the red cell viability exist. The one most frequently used is the determination of the rise in hemoglobin and erythrocytes following blood transfusion and the maintenance of this rise. A method such as this is unsatisfactory since too many variable factors exist in each patient to be able to accurately evaluate any results. A more accurate test is the "Ashby effect"¹¹ used by Schaeffer and Wiener.¹² This test consists of transfusing a patient of known M or N blood grouping with blood containing only the other factor and testing the survival of the transfused red blood cells by means of agglutination test for the heterologous M or N factor. Schaeffer and Wiener found that blood stored for 8 days or less compared

favorably with fresh blood; however, 12-day old blood disappeared rapidly from the blood stream so that by the end of a week approximately 90% of the transfused blood had disappeared. In a further study the same authors¹⁵ found that "the survival time of the transfused cells in the patient's circulation is inversely proportional to the time that the blood was stored before transfusion" and they concluded that "where the need is primarily for erythrocytes, blood stored only a few days is almost equivalent to fresh blood. Blood stored longer than a week is relatively inefficacious."

An index of the viability of transfused erythrocytes can also be obtained by studying one of the main end-products of the destruction of red blood cells in the body, namely urobilinogen, which can be fairly accurately determined in the feces and urine. In using the method of urobilinogen excretion to determine the length of viability of transfused red cells, the type of anemia selected for this study must be one in which a fairly constant rate of hemolysis occurs, *i. e.*, an approximately constant excretion of urobilinogen. Cases of aplastic anemia seemed to satisfy these criteria. The 3 patients chosen received repeated transfusions of blood of varying ages from a few hours to 18 days. The urobilinogen excretion in the urine and stool was determined before and after each transfusion of blood.

Methods. Urobilinogen Excretion. A. Watson's modification of Terwen's method¹⁶ was used for determining the quantitative excretion of urobilinogen in the urine and stools. Stools were collected over a 3- or 4-day period and an average determination for the 3- or 4-day period was made. Urine was collected for 24 to 48 hours in a dark bottle kept on ice with petroleum ether and sodium carbonate as a preservative. Results obtained are expressed in mg. per 24 hours, 50 to 200 mg. being normal in the stool and up to 2 mg. in the urine.

B. Icterus index: The method of Ernst and Förster¹ was used. Acetone-treated plasma was compared directly with potassium dichromate standards as suggested by Soffer and Paulson.¹³

C. Red cell counts were made in the usual manner. Hemoglobin determinations were made with the Sahli hemoglobinometer and Wintrobe's method for packed red cell volume was used.

Clinical and Laboratory Observations. CASE 1. R. S., white female, aged 29, who for 2 years before admission to the hospital complained of marked weakness and dizziness. Although her hair had been gray for 7 years no dyes had been used. Her hemoglobin at that time was 50%. Intensive liver and iron therapy proved of no value. She was admitted to this hospital for diagnosis and treatment. The physical examination on admission revealed no abnormalities other than extreme pallor and slight bleeding from the gums. The tourniquet test, bleeding and coagulation time were within normal limits. Blood examination revealed the following: hemoglobin 38% (Sahli), erythrocytes 1,178,000, white cells 5300, platelets 45,000. The differential was relatively normal with 7% non-segmented neutrophils, segmented neutrophils 50%, lymphocytes 36%, monocytes 7%. Free acid was present in the stomach. The icterus index was 4 (acetone method) and Van den Bergh was negative. Bone marrow aspiration showed an active marrow with a moderate increase in erythroid

elements. A sternal marrow biopsy revealed similar findings. Bilirubin tolerance, galactose tolerance tests, and bromsulphalein tests were normal.

During 18 days 2 transfusions of 5-day-old citrated blood stored at 4° C. and fresh citrated blood were given. Both donors and recipient were Group O.

The excretion of urobilinogen in the urine and stool was determined for a control 4-day period. The fecal urobilinogen was 28.6 mg. per 24 hours and the urinary urobilinogen was present in a quantity too small to be measured accurately. During the first 3-day period, following the transfu-

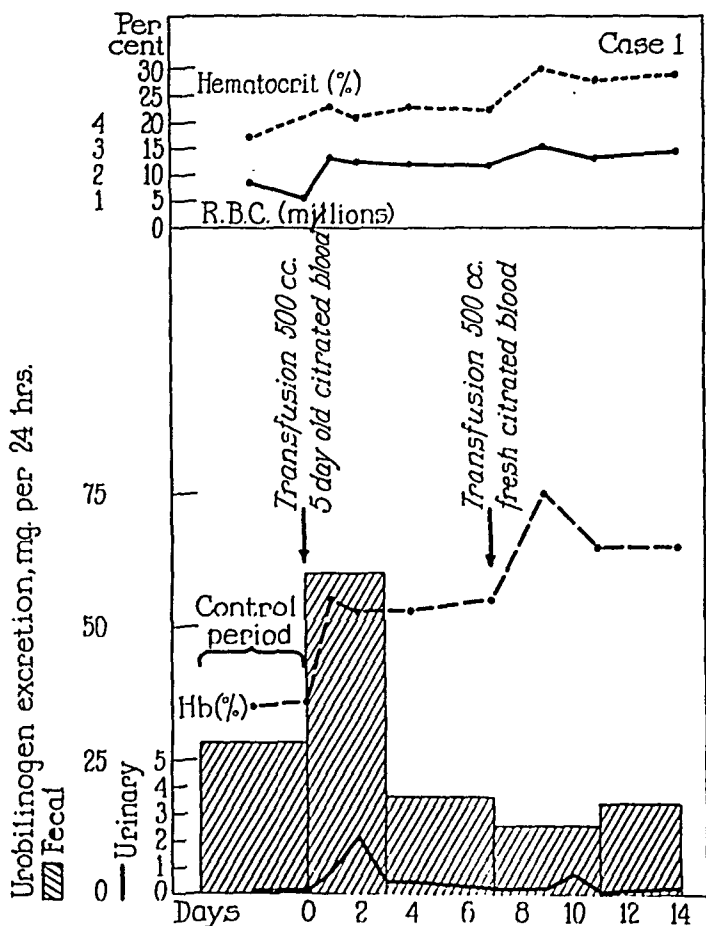


CHART 1.—Case 1. Note immediate rise in urobilinogen excretion following the transfusion of 5-day-old blood, and no increase following the transfusion of fresh blood.

sion of 500 cc. of 5-day-old citrated blood, a definite increase in fecal and urinary urobilinogen did occur. The pigment excretion in the stool was increased to 59.8 mg. per 24 hours and the urinary pigment was increased to 2.12 mg. per 24 hours. By the seventh day following the transfusion, the excretion had returned to the pretransfusion level at which time another transfusion of fresh citrated blood was given. No rise in pigment excretion occurred during the week following this transfusion. The initial hemoglobin of 37% was raised to 65% following the 2 transfusions. No rise in the icterus index occurred and no reaction to either transfusion occurred (Chart 1).

This case, although followed for only a short time, did show that during the first week following the transfusion, fresh blood is not hemolyzed within the body to the same degree as blood stored for 5 days.

CASE 2. M. P., a 70-year-old white female, was first seen at this hospital in September, 1934, at which time she complained of weakness and palpation on excretion. Except for pallor, physical examination was essentially negative. The blood count was as follows: hemoglobin 58%, red cells 2,570,000, white cells 3200, platelets 140,000, with a normal differential. The gastric contents contained free hydrochloric acid and Roentgen ray examination of the entire skeleton was negative. She received intensive liver and iron therapy with no response, and from that time until the present admission, blood transfusions were necessary at regular intervals to combat the anemia. Sternal biopsy revealed islands of active erythropoiesis with numerous erythroblasts, lymphocytes, and few immature cells.

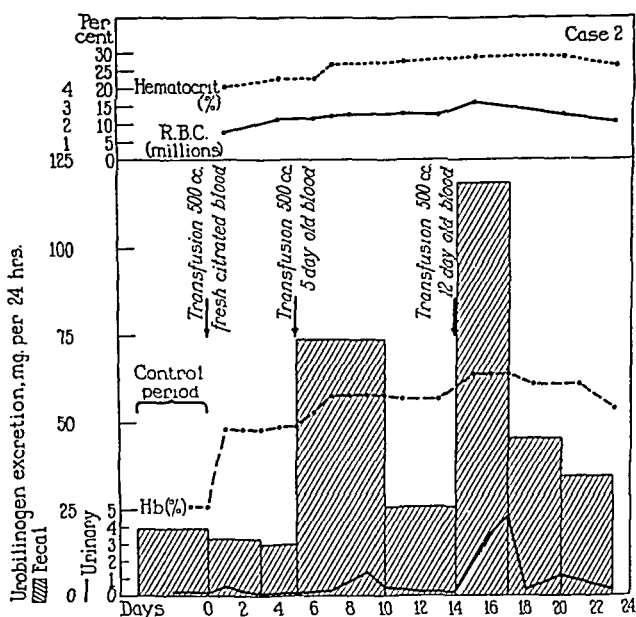


CHART 2.—Case 2. Note the progressive increase in the urobilinogen excretion with the increase in the storage time of bank blood.

All blood chemistry determinations were within normal limits and liver function tests were normal. Pigment excretion studies were started when the patient was admitted with a hemoglobin of 26%. The average daily excretion of urobilinogen was 19.8 mg. per 24 hours in the feces and 0.21 mg. per 24 hours in the urine, an extremely low figure. The patient was given transfusions at various periods of fresh citrated blood, 5-day-old citrated blood, and 12-day-old citrated blood and urobilinogen determinations were made before and after each transfusion.

This case was followed for a period of 25 days. A 500-cc. transfusion of fresh citrated blood induced no rise in the pigment excretion in the urine and stool within a period of 1 week following the transfusion. Five-day-old citrated blood (500 cc.) caused a rise from 14.8 mg. per 24 hours in the fecal urobilinogen to 74 mg. per 24 hours within 3 days following the transfusion and a drop to the pretransfusion level in 7 days. Blood stored for 12 days

caused a marked rise to almost 6 times the pretransfusion level (118 mg. per 24 hours) within 3 days following the transfusion and fell slowly to the original level within a week. In this case the fresh blood was followed by a greater rise in hemoglobin and red cells. The increase in urobilinogen excretion was directly proportional to the age of the blood transfused (Chart 2).

CASE 3. V. G., a 48-year-old Italian housewife, was first seen in July, 1936, because of weakness, shortness of breath, and extreme pallor. The blood count at the time was: hemoglobin 32%, red cells 1,140,000, white cells 2400, segmented neutrophils 52%, lymphocytes 39%, eosinophils 8%, myelocytes 1%. Except for a spleen that was palpable 3 fingers below the costal margin, the physical examination was essentially negative. Free

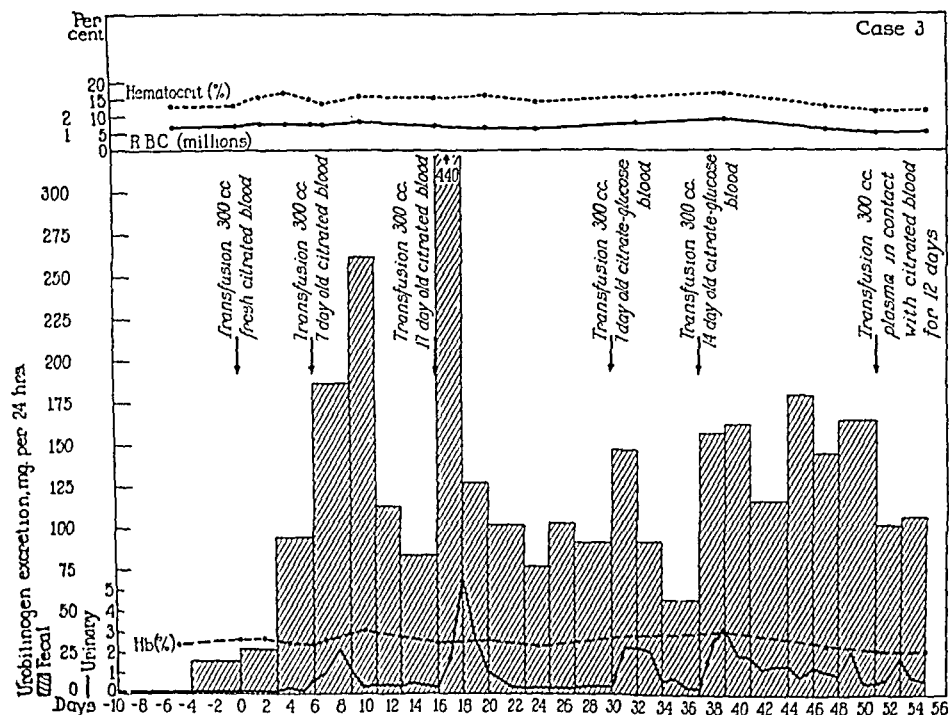


CHART 3.—Case 3. Note the reduction in the urobilinogen excretion following transfusion of blood stored with glucose citrate as the preserving mixture.

acid was present in the stomach contents; and all blood chemistry determinations were within normal limits. A sternal marrow biopsy showed a cellular marrow, with an increase in the immature myeloid elements. The average urobilinogen excretion was 0.45 mg. per 24 hours in the urine and 32 mg. per 24 hours in the feces. Her past history was negative except for the fact that the patient had been using a hair dye for 11 years which contained paraphenylenediamine and m-toluylene diamine. Four years before admission following the administration of this dye the scalp had become inflamed and no further treatments had been given. A diagnosis of aplastic anemia due to the hair dye was made and treatment consisted of liver and iron, female sex hormones and transfusions. No definite remissions occurred except following the transfusions, and these were only temporary. The pigment excretion in the urine and stool remained low and liver function tests (hippuric acid tests, bilirubin tolerance tests and galactose tolerance tests) were within normal limits. The patient was followed in the Out-Patient Department and was admitted on the average of once a month for

blood transfusions. At the time of the present admission, the hemoglobin was 30% with 1,450,000 red cells and a packed cell volume of 13%. Similar studies of the urobilinogen excretion before and after blood transfusion with various aged blood were made.

This case was followed for a period of 60 days during which time 24 fecal and 47 urinary urobilinogen determinations were done (Chart 3). As in the previous cases, fresh blood caused no appreciable rise in the urinary or fecal urobilinogen excretion for the first 3-day period following the transfusion. However, a late rise to 3 times the original level did occur from the fourth to the seventh day following the fresh blood transfusion; 300 cc. of blood were given in every instance. Seven-day-old blood increased the urobilinogen excretion to 260 mg. per 24 hours within 5 days following the transfusion. Five days later the fecal pigment excretion was still elevated, being 84 mg. per 24 hours. With the rise of fecal urobilinogen a like rise in urinary urobilinogen occurred within the first few days after the transfusion. This unquestionably was due to the overloading of the liver with bile pigment and the inability of the liver to excrete this substance. Thus a temporary rise in the icterus index to 15 occurred which rapidly returned to normal within 2 days. A transfusion of 300 cc. of 17-day-old blood caused a marked rise within the first 3-day period to an amount 20 times the original level with a slow return to the pretransfusion level within 2 weeks. Urinary urobilinogen again rose within the first 2 days following the transfusion to 5.6 mg. per 24 hours and returned within 4 days to the initial low level. The overloading phenomenon of the liver with bile pigment is thus again exemplified.

Rous and Turner¹¹ and DeGowin³ and others have shown that glucose when added to the anticoagulant mixture will preserve the red blood cells for a longer period of time. Our own studies have yielded similar results. To test the effect of glucose when added to citrated blood on the urobilinogen excretion, 300 cc. of blood stored for 7 days in DeGowin's glucose citrate mixture was given to this patient. A slight rise in the pigment excretion occurred but was not comparable to the rise following the 7-day-old blood stored with just sodium citrate as the preservative. Blood stored for 14 days with the same glucose citrate mixture produced a rise in pigment excretion that was maintained at 3 times the original level for 2 weeks. A sharp distinct rise that occurred following the use of only sodium citrate as the preserving fluid was not manifested in this case. Likewise the effect of homologous Group 0 plasma on the urobilinogen excretion was also investigated. The patient was given 250 cc. of citrated plasma which had been in contact with red cells for 12 days. This was not followed by any increase in urobilinogen excretion.

Comment. The 3 cases studied fall within the group of refractory anemias as classified by Rhoads.⁸ All 3 cases show cellular marrows with active erythropoiesis. We are not concerned in this paper with the nature of the condition although further investigative work in the group of refractory anemias is being continued. The primary purpose of this study is to evaluate, if possible, the quality and efficacy of bank blood in the treatment of anemias.

It is noteworthy that in spite of the fact that the use of transfu-

sions in the treatment of the anemias can be regarded the most important in the medical field, the literature on the whole is scant. Greppi and Rossi⁶ observed that in hemolytic anemias, fresh blood transfusion is followed by a blood destruction which may be disproportionate to the quantity of the introduced blood, and hence must involve the patient's own blood; and that in other anemias the hemolytic actions involve a small part of only the transfused blood. Introzzi⁷ found that in cases of aplastic anemia the increase of urobilinogen excretion that usually occurs following the fresh blood transfusions does not occur. Barker's² work on the urobilinogen excretion in various blood disorders contained 2 cases of aplastic anemia treated by transfusions in which the hemolytic action was studied for a period of 5 weeks. A sharp increase, immediately after each transfusion, in the excretion of urobilinogen, from 108 to 600 mg. was observed in 1 instance, and to 350 mg. in another; in these instances there was only transient improvement. However, in these cases also, fresh whole blood was used, and in the first instance a transfusion reaction occurred. In the second case an increase in excretion occurred after each transfusion.

In our 3 cases the initial urobilinogen excretion was at an extremely low level, as might be expected because of the low circulating blood volume. Watson^{14a} has found that in most cases of aplastic anemia the excretion is within the limits of normal. Barker² supports the above view and cites only 1 case with a fecal urobilinogen excretion below 50 mg. per 24 hours. Our 3 cases have been chosen because of the low constant level of pigment excretion and because any hemolyzing factor of the patients' own blood could be ruled out.

Since the liver is the most important organ in the excretion of bilirubin, bilirubin tolerance tests were done to determine the capacity of the liver to excrete injected bilirubin. All excretion tests performed with this method were within normal limits, and other liver function tests, as the sodium benzoate, bromsulphthalein and galactose tolerance, also gave normal values. The determination of the urobilinogen excreted in the urine and stool could thus serve as an index of the capacity of the body to utilize this transfused blood. An increased excretion of urobilinogen in the stool means a destruction of blood, either of that introduced by the transfusion or the patient's own blood. Studies on the regenerative index were not done, but we can assume that regeneration was continuing at a rate approximately corresponding to destruction, since anemia was always present with slight variations. In the 3 cases presented here, fresh blood caused little or no increase in pigment excretion during the first week following the transfusion. As blood stored for varying periods of time was given, greater quantities of urobilinogen were excreted almost immediately, and the beneficial action of these bloods was of shorter duration than fresh blood, particularly since the increased excretion was usually continued

over a longer period of time. The addition of glucose to the preserving solution was effective in prolonging the retention and utilization of transfused blood. The observations of the effect of glucose citrate as the preserving solution in bank blood on the urobilinogen excretion leads one to assume that the red cells are in a better state of functional preservation. This is in agreement with many studies, particularly those of DeGowin and his coworkers.³ Plasma itself when transfused caused no increase in the excretion of urobilinogen.

Our results are in agreement with those of Schaeffer and Wiener in that blood stored for less than 7 days may be considered relatively useful for the treatment of anemias.

Conclusions. 1. The excretion of urobilinogen in the stool and urine after transfusion with stored blood is directly proportional to the length of time of blood storage.

2. The use of blood stored for more than 7 days in anemias is inadvisable.

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EFFECT OF LARGE AMOUNTS OF SINGLE VITAMINS OF THE B GROUP UPON RATS DEFICIENT IN OTHER VITAMINS.

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IN multiple deficiency diseases in man, enhancement of certain signs of deficiency following treatment with one single factor has been encountered in pellagrins;⁹ Scandinavian authors^{1,6,8} have re-

ported that treatment of multiple deficiencies with thiamine alone precipitated the appearance of lesions characteristic of nicotinic acid deficiency. In experimentally produced deficiency diseases, György,⁴ Chick *et al.*² and Harris⁵ have shown that in rats maintained on diets deficient in both riboflavin and pyridoxine, the florid dermatitis specific for the lack of pyridoxine does not become evident until riboflavin is supplied. The addition of riboflavin therefore seems to aggravate the manifestations of pyridoxine deficiency. Similar observations have been made on the appearance of deficiency lesions due to the lack of pantothenic acid in young rats which were deficient in both pyridoxine and pantothenic acid.^{3,7} Only after the addition of pyridoxine the characteristic lesions of pantothenic acid deficiency become manifest. Thus, on diets deficient in several members of the vitamin B complex, deficiency diseases may result in which lesions characteristic of the lack of the various single factors might not become conspicuous, and it is generally accepted that the characteristic lesions due to a deficiency in one single factor are more rapidly produced on diets which supply an optimum amount of all other factors of the B complex. It seemed of interest to us to study the manner in which the course and the manifestations of deficiencies due to the lack of one factor of the vitamin B complex may be influenced by the prolonged administration of excessive amounts of the various other members of the B group.

Method. The experiments were carried out on 920 male albino rats. At 3 weeks of age the rats were placed on highly purified diets deficient either in the entire vitamin B complex, or in individual factors such as riboflavin, pyridoxine or pantothenic acid. The rats maintained on the various diets were divided into groups of 20. Every group received a daily supplement of one vitamin in an excessive amount. The amounts, given to each rat by stomach tube, were 1 mg. of either thiamine, riboflavin, or pyridoxine or 10 mg. of either nicotinamide or calcium pantothenate; amounts which represent approximately one hundredfold the maintenance dose. The animals were kept in individual cages, their weights and their symptoms were recorded at frequent intervals. The experiments were concluded after a period of 100 days and autopsies were performed on all animals.

Experimental. *A. Excessive amounts of thiamine with diets free from the entire vitamin B complex.* Sixty rats were placed on a diet consisting of dextrose 68%; casein, vitamin-free, 18%; hydrogenated cottonseed oil (Crisco) 8%; salt mixture, U.S.P. XI, No. 1, 4%; cod-liver oil 2% and supplemented with 1 gm. of choline chloride per 100 gm. of diet. The rats were subdivided into three groups of 20. One group received no supplement, the other groups were fed daily 10 μ g. and 1 mg. of thiamine respectively. Except for the initial 10 days, all animals on this diet failed to gain weight (Chart 1). The group receiving no supplement declined in weight, whereas the rats receiving either 10 μ g. or 1 mg. of thiamine maintained their

weight for a period of 6 weeks. Retarded growth was the most conspicuous manifestation in all groups. In the later stages the animals in the two groups supplemented with thiamine became rather untidy, the fur was matted and dirty, some scaly dermatitis developed, especially on the trunk. No difference in appearance was observed between the group receiving 10 μ g. and that receiving 1 mg. of thiamine. Likewise, the mortality in these two groups was approximately the same (Table 1). Without thiamine, all animals died within 42 days. Supplementation with 10 μ g. of thiamine prolonged the life of 80% of the animals in this group beyond the 42 days; supplementation with 1 mg. daily produced the same result and gave no evidence of harmful effects.

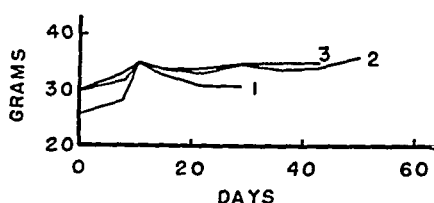


CHART 1.—Growth of rats maintained on a diet free from the vitamin B complex. Each curve represents the average of 20 animals. 1, Basal diet. 2, Receiving a daily supplement of 10 μ g. of thiamine per rat per day. 3, Receiving a daily supplement of 1 mg. of thiamine per rat per day.

TABLE 1.—MORTALITY.

Dietary deficiency.	No. animals.	Daily dose administered.	No. animals dead within:					No. animals surviving.
			28 days.	42 days.	56 days.	70 days.	100 days.	
All B vitamins . . .	20	None	3	20	0
	20	Thiamine, 10 γ	1	4	13	19	20	0
	20	Thiamine, 1 mg.	2	4	13	18	20	0
Riboflavin (none) . . .	40	None	8	24	33	37	37	3
	20	Thiamine, 1 mg.	..	9	16	16	18	2
	20	Nicotinamide, 10 mg.	2	11	19	20	..	0
	20	Pyridoxine, 1 mg.	1	16	18	20	..	0
	20	Ca pantothenate, 10 mg.	..	13	13	14	19	1
Riboflavin (2 μ g. per rat per day) . . .	40	None	..	7	13	15	23	17
	20	Thiamine, 1 mg.	2	5	7	10	16	4
	20	Nicotinamide, 10 mg.	..	4	6	8	12	8
	20	Pyridoxine, 1 mg.	..	2	5	6	12	8
	20	Ca pantothenate, 10 mg.	..	4	6	8	12	8
Pantothenic acid (none) . . .	20	None	5	13	16	18	19	1
	20	Thiamine, 1 mg.	6	14	17	20	..	0
	20	Riboflavin, 1 mg.	6	11	14	18	20	0
	20	Nicotinamide, 1 mg.	9	13	20	0
	20	Pyridoxine, 1 mg.	3	12	17	19	20	0
Pantothenic acid (25 γ per rat per day) . . .	20	None	2	2	3	4	6	14
	20	Thiamine, 1 mg.	1	6	8	8	10	10
	20	Riboflavin, 1 mg.	1	2	3	4	9	11
	20	Nicotinamide, 10 mg.	1	2	3	17
	20	Pyridoxine, 1 mg.	2	2	2	3	3	17

B. Excessive amounts of single vitamins with diets deficient in riboflavin. Rats (360), divided into three equal groups, were placed on a diet consisting of dextrose 34%; cornstarch 34%; casein, vitamin-free, 18%; hydrogenated cottonseed oil (Crisco) 8%; salt mixture, U.S.P. XI, No. 1, 4%; cod-liver oil 2%, and supplemented with 0.8 mg. each of thiamine and pyridoxine, 5 mg. of calcium pantothenate and 100 mg. of choline chloride per 100 gm. of diet. One series did not receive any riboflavin, the other two were given a

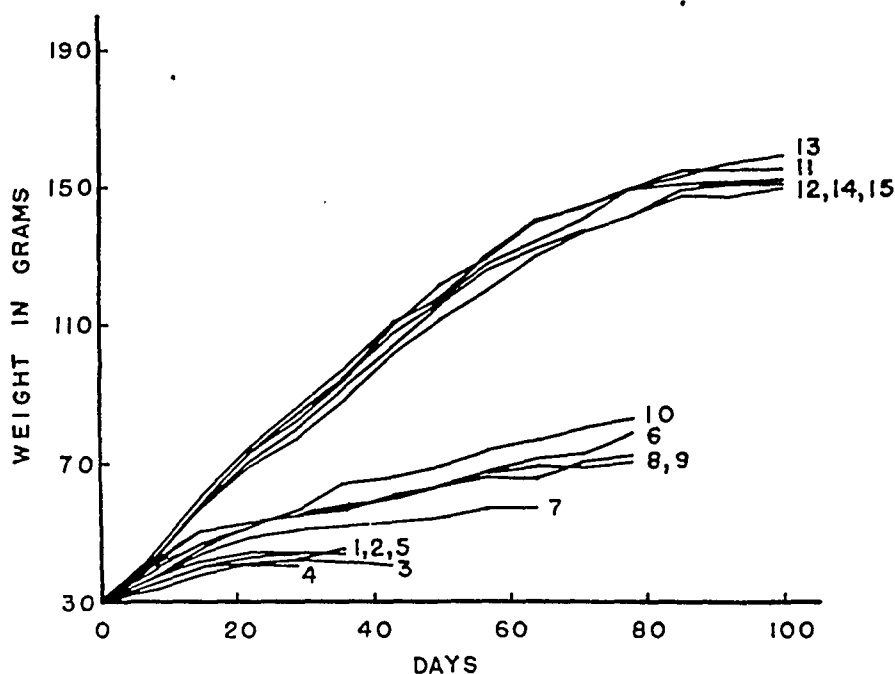


CHART 2.—Growth of rats maintained on diets with and without riboflavin. Each curve represents the average of 20 animals. 1, Basal diet; 2, 3, 4, 5, supplemented with thiamine (1 mg.), nicotinamide (10 mg.), pyridoxine (1 mg.) or calcium pantothenate (10 mg.) respectively per rat per day. 6, Receiving 2 μ g. of riboflavin per rat per day; 7, 8, 9, 10, receiving 2 μ g. of riboflavin and supplemented with thiamine (1 mg.), nicotinamide (10 mg.), pyridoxine (1 mg.) or calcium pantothenate (10 mg.) respectively per rat per day. 11, Receiving 10 μ g. of riboflavin per rat per day; 12, 13, 14, 15, receiving 10 μ g. of riboflavin and supplemented with thiamine (1 mg.), nicotinamide (10 mg.), pyridoxine (1 mg.) or calcium pantothenate (10 mg.) respectively per rat per day.

daily supplement of 2 μ g. and 10 μ g. of riboflavin respectively, both amounts being below the requirement of 20 to 30 μ g. necessary for optimum growth on this diet. Each of the three series was subdivided into one group of 40 animals receiving no further supplement and four groups of 20 animals each receiving excessive amounts of thiamine (1 mg.), nicotinamide (10 mg.), pyridoxine (1 mg.) or pantothenic acid (10 mg.) respectively. The average growth of the animals in the fifteen different groups is shown in Chart 2.

All animals receiving no riboflavin (Chart 2, Group 1-5) gained about 13 gm. during the first 3 weeks, after which period their weights became stationary. There was no significant difference between the group receiving no supplement and those receiving excessive amounts of the other B vitamins. Manifestations of riboflavin deficiency such as thinning of the fur, generalized scaly dermatitis and sticky exudate on the eyelids and especially on the medial canthus of the eye appeared at about the same time and to the same degree in all animals. The mortality of the rats, as recorded in Table 1, was not significantly different in the various groups. Only 6 rats survived the test period of 100 days, 3 in the group receiving no additional vitamin, 2 receiving thiamine and 1 receiving calcium pantothenate.

Addition of 2 μ g. of riboflavin per rat per day to the second series of rats on the riboflavin-free diet resulted in weight gains of about 40 to 50 gm. in the average for a period of 10 weeks (Chart 2, Group 6-10). However, the amount of riboflavin was too small to support life for more than 11 weeks for the majority of the rats. Additional feeding of massive doses of nicotinamide, pyridoxine or pantothenic acid (Groups 8, 9, 10) did not influence the weight gain of the rats. The rats receiving 1 mg. of thiamine daily (Group 7) did not gain in weight at the same rate as the other groups. A somewhat higher mortality (see Table 1) was encountered in the group fed thiamine; 50% of the animals died within a 10-week-period and only 20% were still living after 100 days. On the other hand, 40% of the group receiving no additional vitamins as well as of the groups receiving nicotinamide, pyridoxine or pantothenic acid survived the test period. The appearance and severity of the deficiency lesions due to the insufficient amount of riboflavin were comparable in all groups of this series.

To the members of the third series of experiments 10 μ g. of riboflavin were given daily and the same scheme of feeding additional vitamins to the various groups as in the first two series was carried out. As evidenced by Chart 2 (Group 11-15), all rats in this series gained weight at the same rate of approximately 1.5 gm. per day. All rats, with the exception of 2 animals accidentally killed, survived the test period. No definite lesions due to the relative deficiency in riboflavin were observed in any of the various groups.

C. Excessive amounts of single vitamins with diets deficient in pantothenic acid. Rats (300), divided into three equal groups, were placed on a basal diet consisting of dextrose 68%; casein, vitamin-free, 18%; hydrogenated cottonseed oil (Crisco) 8%; salt mixture, U.S.P. XI, No. 1, 4%; cod-liver oil 2%, and supplemented with 0.8 mg. each of thiamine, riboflavin and pyridoxine, 10 mg. of nicotinamide and 100 mg. of choline chloride per 100 gm. of diet. One series of animals did not receive any pantothenic acid; another series received a

daily supplement of 25 μ g. of calcium pantothenate per rat, an amount which is insufficient for optimum growth. The third series was given 100 μ g. of calcium pantothenate, an amount which meets

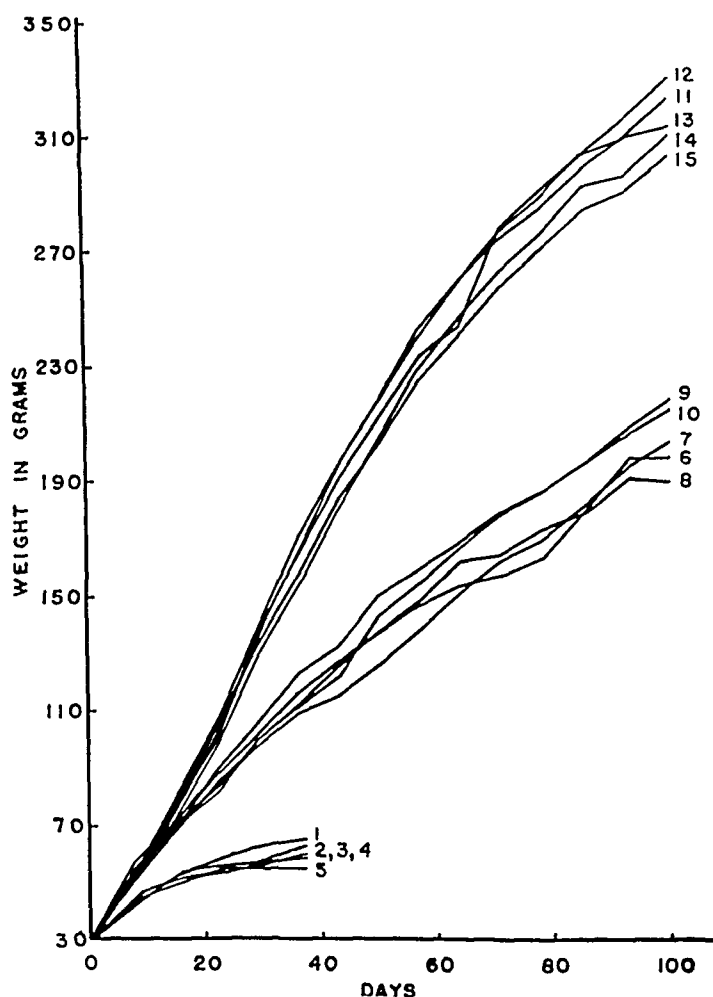


CHART 3.—Growth of rats maintained on diets with and without pantothenic acid. Each curve represents the average of 20 animals. 1, Basal diet; 2, 3, 4, 5, supplemented with thiamine (1 mg.), riboflavin (1 mg.), nicotinamide (10 mg.) or pyridoxine (1 mg.), respectively, per rat per day. 6, Receiving 25 μ g. of calcium pantothenate per rat per day; 7, 8, 9, 10, receiving 25 μ g. of calcium pantothenate and supplemented with thiamine (1 mg.), riboflavin (1 mg.), nicotinamide (10 mg.) or pyridoxine (1 mg.), respectively, per rat per day. 11, Receiving 100 μ g. of calcium pantothenate per rat per day; 12, 13, 14, 15, receiving 100 μ g. of calcium pantothenate and supplemented with thiamine (1 mg.), riboflavin (1 mg.), nicotinamide (2 mg.) or pyridoxine (1 mg.), respectively, per rat per day.

the requirement for optimum growth in young rats maintained on this diet.¹⁰ Subdivision of the three series of animals into five groups of 20 each and feeding of large daily doses of single vitamins (either 1 mg. of thiamine, riboflavin or pyridoxine or 10 mg. of nico-

tinamide respectively) followed a scheme similar to that used in the experiments with the riboflavin-deficient rats.

The animals of the first series which received no pantothenic acid gained between 25 and 30 gm. during the first 3 weeks. The weight curve for Group 1 receiving no additional vitamin and those for Group 2-5 receiving large supplements of either thiamine, riboflavin, nicotinamide or pyridoxine are practically the same (Chart 3, Group 1-5). Rats of all groups manifested loss of hair and porphyrin deposits on the fur, especially on the whiskers, signs characteristic of pantothenic acid deficiency. Adrenal hemorrhages were found in all groups. Likewise, no difference was observed in the mortality of the different groups (Table 1); more than half of the animals in each group died within 6 weeks.

The second series of animals received a daily supplement of 25 μ g. of calcium pantothenate. No significant difference in the rate of growth was found between Group 6 receiving no additional vitamins and any one of those four groups (7-10) receiving large vitamin supplements (Chart 3, Group 6-10). Fourteen animals of the group receiving no additional vitamins survived the test periods; only 10 and 11 animals in the groups fed excess thiamine or riboflavin respectively survived. On the other hand, the rats fed additional amounts of pyridoxine or nicotinamide survived in greater numbers than those of the control group (Table 1). The deficiency lesions observed in this series were confined to a moderate degree of alopecia and some rusty spots (porphyrin) on the fur. They were of comparable extent in all groups. No adrenal hemorrhages were found on gross examination at autopsy.

All animals in the third series supplemented with 100 μ g. of calcium pantothenate gained at a rate of approximately 3 gm. per rat per day (Chart 3, Group 11-15) and no difference was seen between the control (Group 11) and the other groups receiving the large amounts of other vitamins (Group 12-15). All rats presented a normal healthy appearance throughout the test period.

D. Excessive amounts of thiamine or pantothenic acid with a diet free from pyridoxine. Rats (200) were placed on a diet consisting of dextrose 68%; casein, vitamin-free, 18%; filtered butterfat 8%; salt mixture, U.S.P. XI, No. 1, 4%; cod-liver oil 2%, and supplemented with 0.8 mg. each of thiamine and riboflavin, 10 mg. of nicotinic acid, 5 mg. of calcium pantothenate and 100 mg. of choline chloride per 100 gm. of diet. A group of 100 animals receiving no further supplements served as a control for two groups of 50 rats which were given a daily supplement of 1 mg. of thiamine or 10 mg. calcium pantothenate respectively.

No difference was observed between the rats of the three groups. All animals became stationary in weight after 4 weeks at 50 to 55 gm. The first signs of scaliness on the paws became noticeable

simultaneously in the different groups during the third week. The characteristic dermatitis of pyridoxine deficiency involving the paws, ears and snout progressed at a comparable pace in all animals.

Discussion and Summary. Large amounts of individual factors of the vitamin B complex were fed over periods extending to 100 days to rats subsisting on diets inadequate in one or more factors of the B complex. The rats were maintained on highly purified diets free from either riboflavin, pyridoxine, pantothenic acid or the entire B complex. Other rats subsisted on diets partially deficient in riboflavin or pantothenic acid.

Daily feeding of large amounts of single crystalline vitamins of the B group did not significantly influence the growth rate of the deficient animals, nor the appearance of severity of the deficiency lesions characteristic of the missing factors. Furthermore, the mortality of rats receiving large amounts of additional vitamins did not differ significantly from those receiving no further supplement.

Daily feeding of either 10 μ g. or of 1 mg. of thiamine to rats on diets free from all B vitamins produced the same effect in maintaining weight and in prolonging the life of the animals. The addition of 1 mg. of thiamine daily resulted in somewhat smaller weight increase and higher incidence of mortality in rats receiving an insufficient amount (2 μ g) of riboflavin daily. However, in another group of animals receiving suboptimal amounts of riboflavin (10 μ g. daily), no such effect of thiamine could be found. All other findings were deviations within the normal range.

Conclusions. Prolonged administration of large amounts of individual vitamins of the B group to rats subsisting on diets either entirely free from or partly deficient in one or more factors of the vitamin B complex failed to aggravate the manifestations of the deficiency state.

Our experiments present no evidence of adverse effects following the administration of an excess of individual vitamins in the presence of deficiencies of other vitamins of the B complex.

We wish to express our appreciation to Dr. Henry Siegel for performing the autopsies of the animals.

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STUDIES OF THE EFFECTS OF MILLION VOLT ROENTGEN RAYS, 200 KILOVOLT ROENTGEN RAYS, RADIOACTIVE PHOSPHORUS, AND NEUTRON RAYS BY THE MARROW CULTURE TECHNIQUE.*

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THIS paper presents data, obtained by the method of human marrow culture,⁸ on the comparative effectiveness of million volt Roentgen rays, 200 kv. Roentgen rays, neutron rays, and beta rays emitted by radioactive phosphorus. This method permits quantitative controlled studies of the effects of physical and chemotherapeutic agents on a known number of known types of living human cells. For example, in previous publications by this method⁹ it has been shown that the action of Roentgen rays appears to inhibit the onset of mitotic and amitotic division; that the ratio of the effect on the highly susceptible lymphocytes to that on the less susceptible progranulocytes (promyelocytes) is the same with a small exposure to 50 r as with a larger exposure to 400 r; that increasing the exposure from 50 r to 400 r increases the effect 1.7 times instead of 8 times; and that the inhibitory effect on leukemic progranulocytes is similar to that on non-leukemic progranulocytes, although the rate of decrease is more rapid. This latter was interpreted as being due to a higher rate of cell division for the leukemic progranulocytes. It has also been shown in interchange of media between irradiated and non-irradiated marrow cultures that there is no evidence of an indirect action of the Roentgen rays, but the effects could all be explained if the action of the irradiation was directly on those cells capable of mitotic or amitotic division to inhibit the onset of division.

* Aided by grants from the Dazian Foundation, the John C. Higgins Experimental Medicine Fund, and the Columbia Fund for Medical Physics of the Columbia Foundation.

Read before the Biometrics Section of the American Statistical Association, Berkeley, Calif., December 31, 1941.

The literature on the biologic effects of Roentgen rays has been reviewed by Scott,¹³ Duggar,⁴ and Selling and Osgood;¹² that on neutron rays has been reviewed by Aebersold and Lawrence;³ and that on radioactive phosphorus has been reviewed by Scott and Lawrence¹⁴ and Lawrence, Scott and Tuttle.¹⁴ An extensive review of the literature will not be given, therefore, in this paper.

Method. In each experiment, about 10 cc. of human marrow obtained by sternal puncture⁷ were introduced into a 50 cc. vaccine vial containing 25 cc. of citrated balanced salt solution. After manipulation to eliminate most of the non-nucleated erythrocytes, the final culture contained about 100,000,000 nucleated marrow cells suspended in about 50 cc. of a medium consisting of about 35% human umbilical cord serum obtained from the fetal side of the placenta and 65% balanced salt solution similar in composition to cerebrospinal fluid. This was thoroughly mixed, and after removal of a sample for initial total and differential cell counts equal volumes were placed in each of 4 to 6 vaccine vials. All manipulations were made with syringe and needle through 70% alcohol on the vaccine vial caps. The vials containing the identical cultures were then sent by Air Express to the W. H. Crocker Radiation Laboratory, University of California in Berkeley where, under the supervision of Dr. P. C. Aebersold, Dr. J. H. Lawrence, and Dr. L. A. Erf, the cultures were treated with neutron rays, million volt Roentgen rays, 200 kv. Roentgen rays, or radioactive phosphorus, 1 vial always being left untreated as a control. The vials were then returned by Air Express, placed in the incubator at 37° C., and at intervals samples were removed for total and differential cell counts. The medium was changed every 24 to 48 hours. In some experiments identical vials of cultures were kept in Portland at room temperature or in the pocket of one of the investigators as an additional control. These always showed counts within the limits of experimental error identical with that of the control vial which had been shipped to Berkeley and back again. This technique assured that there was the same number of the same type of cells in the same volume of identical medium in each vial and that the only variable introduced was the ionizing irradiation.

The factors used in the irradiation were as follows: For the million volt Roentgen ray irradiation, the million volt tube in the Roentgenologic Division at the University of California Hospital in San Francisco* was used with 2 mm. of lead added filter, an 80 cm. target to liquid distance, and an intensity of approximately 20 r per minute. The exposure was measured by a Victoreen condenser r-meter, the total exposure being 200 r. The half-value layer for these Roentgen rays was 9 mm. of copper. The 200 kv. irradiation was given with a 200 kv. constant potential machine, with an added filter of 0.2 mm. of tin and 0.25 mm. of copper, an 80 cm. target to liquid distance, and an intensity of approximately 15 r per minute measured by the same Victoreen condenser r-meter. The half-value layer in copper was 1.4 mm. in the first series of experiments in which million volt and 200 kv. Roentgen rays and neutron rays were compared. For the other experiments the Roentgen ray irradiation was given with a 220 kv. Maximar apparatus† in the Radiation Laboratory in Berkeley. The factors were 220 kv. peak voltage, 15 ma., 2 mm. of copper added filter, and 60 cm. target to liquid distance, a half-value layer of 2.3 mm. of copper. This exposure as measured inside one of the empty vials from which the bottom had been cut off was 31 r per minute. One vial from each culture

* We are indebted to Dr. R. S. Stone for his collaboration in these studies.

† This apparatus was made available through the courtesy of the General Electric X-ray Corporation.

in this series of experiments received 400 r and 1 vial received 60 r of X-radiation.

All irradiation with neutrons was done under the same conditions. The neutrons were generated by the 60 inch cyclotron at the Radiation Laboratory in Berkeley by bombarding beryllium with 16 million volt deuterons. The neutrons were collimated to a 10 by 15 cm. field at 100 cm. from the beryllium target by the standard arrangement used for treating patients.¹⁵ The beam was filtered through 3 cm. of lead to suppress gamma rays. The exposure was measured with an 100 r size Victoreen condenser r-meter, and the readings were called "n" instead of "r" when the meter was exposed to neutrons. In the first series of experiments, 50 n of neutron rays

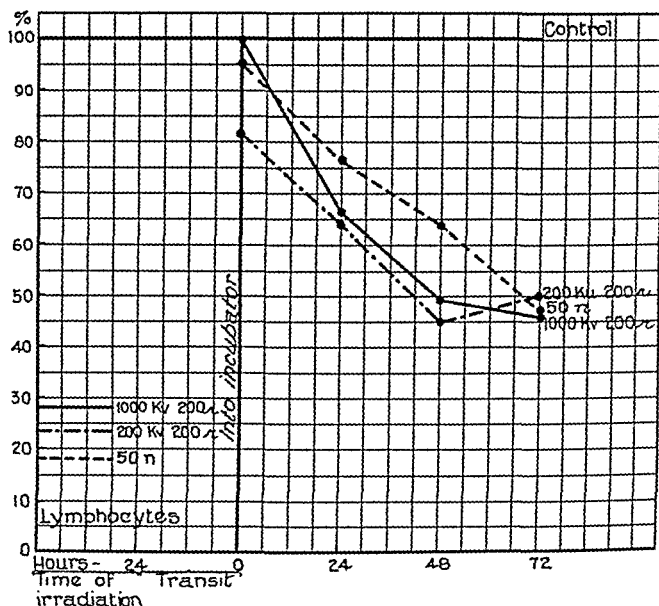


FIG. 1.—Comparative effects on lymphocytes in marrow cultures of 200 r of Roentgen rays at 1000 kv. and at 200 kv. and of 50 n of neutron rays. The points on the curves represent the weighted averages of the absolute number of lymphocytes in the corresponding vials of the 4 experiments expressed in percentage of the absolute number of lymphocytes in the 4 controls at the same time. The time of irradiation was 24 to 48 hours before the cultures were put in the incubator. They were in transit from Berkeley to Portland during the 24 hours preceding the time they were placed in the incubator. The factors used in the irradiation are given in the text.

were given to 1 vial to compare with other vials from each of these experiments which received 200 r of 220 kv. Roentgen rays and 200 r of million volt Roentgen rays. In the second series of experiments, 1 vial from each culture received 15 n of neutron rays to compare with the vial in the same experiment that received 60 r of Roentgen rays, and 1 vial was given 100 r of neutron radiation to compare with the vial from the same culture receiving 400 r of 220 kv. Roentgen rays.

The radioactive phosphorus was prepared with the 60 inch cyclotron and introduced into the vials in the form of disodium phosphate, Na_2HPO_4 . The radioactive phosphorus gives out only beta rays (no gamma or alpha rays) whose maximum energy is about 1.7 million electron volts. The activity was measured with a Lauritsen electroscope. From physical data²

it was calculated that an average of 1 microcurie uniformly distributed through 1 cc. of culture should produce the same ionization in a 24 hour period as an exposure to 35 r of Roentgen rays. On this basis, the amount which should produce the same ionization as would 400 r of Roentgen rays in a 24 hour period was calculated and introduced into 1 vial from each experiment of the third series. An equal volume of the same concentration of non-radioactive disodium phosphate was introduced into the control vial at the same time. On return of the cultures about 24 hours after irradiation the vials were centrifugated and the medium removed and fresh medium not containing radioactive phosphorus but identical in composition

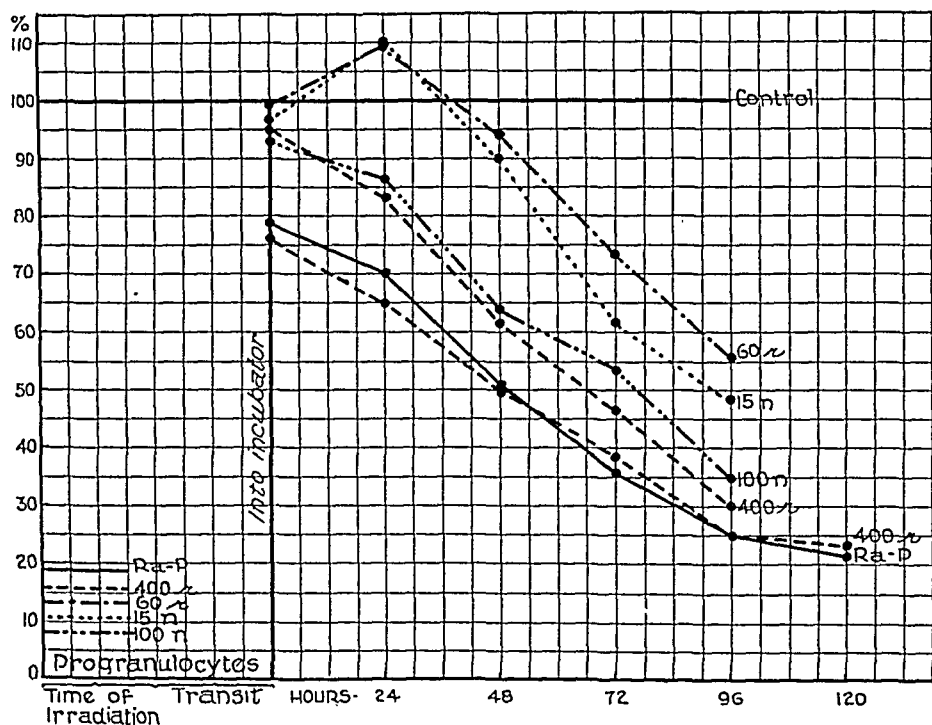


FIG. 2.—Comparative effects on progranulocytes of 60 r of Roentgen rays at 220 kv., 15 n of neutron rays, 100 n of neutron rays, and 400 r of Roentgen rays at 220 kv. (based on the weighted averages of 13 experiments). Also of 400 r of Roentgen rays at 220 kv. and an average of 11.4 microcuries of radioactive phosphorus per cc., acting over a period of 24 hours (based on 6 experiments). Compare these curves with the corresponding curves for lymphocytes from the same two series of experiments shown in Figure 3. The factors used in the radiation are given in the text.

with the medium introduced into the other vials of the same experiment was added. The time of removal of the medium was noted, and the removed medium was shipped back to the Radiation Laboratory where quantitative studies indicated that over 90 per cent of the radioactive phosphorus was recovered.

The total nucleated cell counts were done by the cerebrospinal fluid cell counting method.¹⁶ In each instance, about 400 cells were counted, so that the standard deviation of these individual determinations was about \pm or -5% . The differential cell counts were done on Wright's stained smears, and the cells were classified according to the criteria given in the "Atlas of Hematology" by Osgood and Ashworth.¹⁰ Wherever possible, enough cells were enumerated so that at least 20 of each type of cell were counted. This often necessitated counting several thousand cells. All of

the determinations were made by one of us (E. A. P.), so that there should be a minimum of variation in the technique. From the total and differential cell counts, the absolute numbers of each type of cell at each time period in each of the cultures was determined. The absolute number of cells of each type in each vial of each experiment was plotted on graph paper. From these graphs the absolute number of each type of cell in each vial was read off for 24, 48, 72, 96 and 120 hours after the culture was placed in the incubator. Since the total nucleated cell counts decrease in the controls

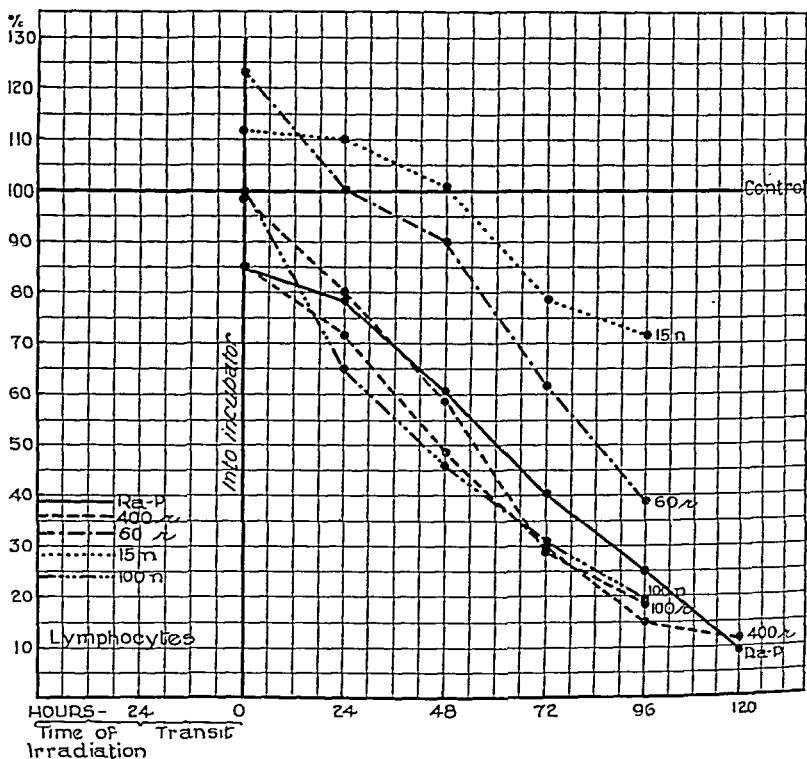


FIG. 3.—Comparative effects on lymphocytes of 60 r of Roentgen rays at 220 kv., 15 n of neutron rays, 100 n of neutron rays, and 400 r of Roentgen rays at 220 kv. (based on the weighted averages of 13 experiments). Also of 400 r of Roentgen rays at 220 kv. and an average of 11.4 microcuries per cc. of radioactive phosphorus, acting over a period of 24 hours (based on 6 experiments). Compare these curves with the corresponding curves for progranulocytes from the same two series of experiments shown in Figure 2. The factors used in the radiation are given in the text.

while the absolute numbers of some cell types increase and others decrease during the time of irradiation it is necessary to compute the numbers of a particular cell type in an irradiated vial in percentage of the same type of cell in the non-irradiated control in order to show clearly the effects of irradiation. The points on the curves shown in Figures 1 to 3 were, therefore, computed as follows: The absolute number of lymphocytes per c.mm. for each time period from 0 to 96 or 120 hours for the control in each experiment was added together, which gave the total number of lymphocytes per c.mm. in all of the controls of the series of experiments. The total absolute

number of lymphocytes per c.mm. for the vials which received the same type and amount of irradiation from the same series of experiments were added in the same way, and this total was divided by the total of the same type of cell in the control and multiplied by 100 to give the absolute number of lymphocytes from all experiments receiving the same dose and type of irradiation in percentage of the total absolute number of lymphocytes in the corresponding controls. In other words, this gave a weighted average of the percentage of lymphocytes in all of the cultures receiving one type of irradiation in terms of the numbers of the same type of cell in the control at the same time period. Consequently, if there were no deviations from the control the figure should be 100% within the limits of experimental error of the method, and any deviation from the 100% line greater than the experimental error of the method must be due to the effect of the irradiation given. The results were similarly computed for the other types of cells and are plotted in Figures 1 to 3. Note that the time, not the exposure, is plotted on the X-axis and that the whole curve represents the effects of a particular wave length, exposure, and modality of irradiation relative to the control at the same time. The results for the granulocytes (myelocytes), metagranulocytes (metamyelocytes), rhabdocytes (staff cells), and lobocytes (polymorphonuclear neutrophils) were not plotted, since our previous work⁹ showed that only the lymphocytes and granulocytes divide and that the more mature cells of the granulocyte series follow the curve of the progranulocytes but leave the control line at progressively later intervals.

Three series of experiments were performed. In the first series, consisting of 4 experiments, 200 r of X-radiation was given at 200 kv. to 1 vial, 200 r at 1000 kv. to another vial, and 50 n of neutron rays was given to a third vial. The fourth vial from each experiment constituted the control (see Fig. 1). Only 2 experiments out of the first series had enough progranulocytes to count, so that the curves were not of sufficient statistical significance to be worth including.

The second series of experiments included the data from 13 experiments in which for each experiment there was a control, a vial which received 60 r of X-radiation with the 220 kv. machine, 1 which received 15 n of neutron radiation, another which received 100 n of neutron radiation, and a fifth which received 400 r of X-radiation with the 220 kv. machine. Both progranulocytes and lymphocytes were plotted. The results are shown in Figures 2 and 3.

The third series of experiments consisted of 6 experiments in which there was a control culture, 1 culture which received 400 r of X-radiation with the 220 kv. machine, and another culture which received beta radiation from an average of 11.4 microcuries of radioactive phosphorus for a 24 hour period. Data from these 6 experiments are plotted for progranulocytes and lymphocytes in Figures 2 and 3.

Comment and Results. Note from Figures 1 to 3 that the curves for lymphocytes and progranulocytes in all experiments approach a straight line within the experimental error of the method. They fall from the control level at the time the cultures were put into the incubator until the last determinations were made. The straight line character of the drop was similar to that noted in all previous experiments with irradiation by the same method for lymphocytes and progranulocytes and fits well with the theory based on our previous work that irradiation inhibits the onset of amitotic division in the lymphocytes and mitotic division in the progranulocytes.

The curves in these experiments at first sight appear to differ from the curves in the previous experiments in that in Figures 1 to 3 the decrease in lymphocytes and progranulocytes begins many hours after the time of irradiation; whereas, in previous experiments the decrease began immediately after irradiation. This is apparently explained, however, by the fact that in the previous experiments the cultures were placed in the incubator immediately after irradiation, and in these experiments the cultures were not placed in the incubator until after they had been returned from Berkeley. In both series of experiments, therefore, the decrease relative to the control began immediately after the cultures were placed in the incubator. The most plausible explanation for this difference seems to be that during the time of transit of the cultures from Berkeley to Portland after irradiation they were at the temperature of the outside air or at room temperature and, consequently, the cells in the controls did not divide. If the action of irradiation were to inhibit the onset of cell division no difference from the control would be expected until the cultures were placed in the incubator and cell division began. Although the effect obviously occurred at the time of irradiation no morphologic or quantitative differences relative to the control were detected until the cultures had been incubated, even though 24 to 48 hours had elapsed since the time of irradiation. Since less than 1% of the cells were in process of division during irradiation with roentgen or neutron rays, it would seem impossible to explain the major effect as due to the action of ionizing irradiation during the time of cell division.

In each of the irradiated cultures, whether irradiated with neutron rays, Roentgen rays, or the beta rays emitted by radioactive phosphorus, a few large bizarre cells were noted after incubation. These were interpreted as representing cells which had undergone mutation preventing normal development.⁵ No other morphologic differences between the irradiated cultures and the non-irradiated controls were noted. There were no more disintegrated cells, such as are seen in large numbers when toxins or poisons are added to marrow cultures, in the irradiated cultures than were in the controls. This suggests that the irradiation did not alter the death rate of the cells as compared with the death rate in the corresponding non-irradiated controls. Since the cell population decreased, it must have been the rate of cell division, or "birth rate," which was chiefly affected.

Note from Figure 1 that there was apparently no significant difference in the effect on the rate of cell decrease between exposures of 200 r of *X*-radiation given at 200 kv. or at 1000 kv., nor between 50 n of neutron rays and 200 r of *X*-radiation. In previous experiments² no significant difference was found between the effects of 400 r of *X*-radiation given at 200 kv. with a half-value layer of 1.54 mm. of copper and 400 r given at 140 kv. with a half-value layer of 0.36 mm. of copper. It would appear, then, that the effect

of Roentgen rays depends on the amount of ionization produced in the region of the cells and not on the wave length. Consequently, if there is any advantage in the use of million volt Roentgen rays it would have to arise from a superiority of depth dosage¹ or a decrease of skin damage.¹¹

Note from Figures 2 and 3 that 100 n of neutron rays and 400 r of 220 kv. Roentgen rays had the same effect within the limits of error of the method on progranulocytes and on lymphocytes, and that the effect on lymphocytes of the same exposure to irradiation was somewhat greater than on progranulocytes. There also appears to be no significant difference between the effects on progranulocytes of 15 n of neutron rays and 60 r of Roentgen rays, but at first sight it would appear that 15 n of neutron rays has less effect on lymphocytes than 60 r of Roentgen rays. However, at 96 hours the counts in the cultures were so low that statistical analysis shows that this difference is less than one standard deviation, so that it is probably not significant. From the data in Figures 1 and 2 it may be concluded, therefore, that the ratio of exposure, $\frac{r}{n}$ for lymphocytes and progranulocytes as irradiated in the marrow cultures is approximately 4. This value lies near the center of the range, 2 to 10, of reported values³ for the ratio, $\frac{r}{n}$.

Note from Figures 2 and 3 that 400 r of Roentgen irradiation with the 220 kv. machine and an average beta ray activity of 11.4 microcuries per cc. of radioactive phosphorus acting over a 24 hour period had the same effect on progranulocytes and lymphocytes within the limits of error of the method. From these data it would appear that exposure over a period of 24 hours to an average beta ray activity of 1 microcurie of radioactive phosphorus per cc. has about the same effect as 35 r of Roentgen rays on living human lymphocytes and progranulocytes in marrow cultures. This is the same factor which was computed from physical data for the relative ionization by radioactive phosphorus and Roentgen rays.² Since the radiation with radioactive phosphorus was continuous over a 24 hour period, whereas the 400 r of 200 kv. X-radiation was given in the course of about 13 minutes, it is apparent that in this case there was little difference in the effect of a given amount of ionizing irradiation whether given in a short period of time or over a much longer period.

The theory advanced on the basis of previous data obtained by the marrow culture technique would appear to fit well with the data obtained in these experiments. These data would appear to justify extending it to other wave lengths and modalities of ionizing irradiation. This theory is that the action of ionizing irradiation in the doses employed in clinical therapy is chiefly to inhibit the onset of mitotic and amitotic division in cells capable of such division. In addition, such ionizing radiation tends to produce somatic mutations in some

cells. In the marrow cells studied the radiosensitivity of a particular cell type appears to depend on the rate of cell division and the life span. The more frequent the cell division and the shorter the natural life span, the more sensitive is the cell type, and *vice versa*.

If the theory of inhibition of cell division is correct, certain facts must follow. There should be an upper limit of dose radiation for each cell type, beyond which increase in the amount of radiation has no further effect on the slope of the curve representing the time rate of decrease of the population, assuming of course that the doses are considerably below the excessively large doses necessary to produce direct killing of cells. This limit would correspond to the complete inhibition of cell division in all cells of that type. For example, if the life span of the lymphocyte is assumed to be 24 hours and the action of ionizing radiation is only to inhibit cell division and not to kill lymphocytes, the slope of the curve of decrease in lymphocytes could never be made more precipitous than a line drawn from the 100 per cent line at zero time to the zero line at 24 hours. This point is now under investigation. Cells incapable of division show no effect from irradiation with exposures to this order of magnitude, except those secondary to the effects on other cells which could have divided and matured to this stage. This has already been demonstrated to be true for the neutrophil lobocytes which have a natural life span in marrow cultures of 48 to 90 hours⁶ and have never been observed to divide but show no significant difference from the counts in the control vials until after 72 to 96 hours.⁹ Quantitative effects of irradiation could not be accurately evaluated unless the proper time were chosen. This time must be determined from the beginning of the period when conditions suitable for cell division are instituted and not from the time of irradiation, since no effects should be observed until the cells begin to divide. That this is true is shown by comparison of the curves for 400 r of radiation when incubation was begun immediately after irradiation⁹ with those in Figures 2 and 3 when incubation was delayed.

Summary. Controlled quantitative studies of biologic effects of Roentgen rays produced with 1000 kv. apparatus, of Roentgen rays produced with 200 kv. apparatus, of beta rays (average 600 kv.) emitted by radioactive phosphorus, and of neutron rays were made by the technique of human marrow culture. An exposure to 200 r of 200 kv. Roentgen rays had similar effects to an exposure to 200 r of million volt Roentgen rays on lymphocytes. An exposure to 50 n of neutron rays had similar effects to an exposure to 200 r of Roentgen rays given at 200 kv. or 1 million volts. An exposure to 15 n of neutron rays had similar effects on both lymphocytes and progranulocytes to an exposure to 60 r and 400 r respectively of Roentgen rays given at 220 kv. The exposure ratio, $\frac{r}{n}$, for lymphocytes and progranulocytes in marrow cultures is approximately 4. One microcurie average of radioactive phosphorus distributed through

1 cc. of human marrow culture acting for a period of 24 hours has an effect similar to 35 r of high voltage Roentgen rays on lymphocytes and progranulocytes. These effects and the straight line character of the drop may all be explained if the major action of the ionizing radiation is to inhibit the onset of mitotic and amitotic division of the cells receiving the irradiation.

The authors are deeply indebted to Dr. J. H. Lawrence and to Dr. E. O. Lawrence for their coöperation and interest in this study.

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PATHOLOGIC CHANGES IN THE BRAINS OF DOGS GIVEN REPEATED ELECTRICAL SHOCKS.

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NUMEROUS studies of both experimental and clinical material have shown that rather definite pathologic tissue changes result from shock therapy with insulin and with metrazol. In view of the

recent extensive use of electrical shock in the treatment of psychoses, we were led to undertake the following investigation with the object of comparing the brain changes induced by this modality with those produced by the above-mentioned convulsant agents.*

Procedure. Convulsions were repeatedly induced in a series of 12 mongrel dogs by the application of an alternating electrical current. The equipment† was the same as that used by the Department of Psychiatry in electrical shock therapy. The electrodes were applied over shaved areas of the skin superior to the zygomatic arch in the temporoparietal region, external to the motor area of the brain. Shocks were applied at a potential of 80 volts and a current strength of 200 ma.; the duration of the individual shocks was 0.15 second.‡ Shocks were administered at 3 to 5 day intervals.

The total number of shocks given each animal is shown in Table 1. For the most part the animals were given the number of shocks which are administered to patients. Individual animals varied considerably in respect to the severity of the convulsive manifestations induced by the alternating current applied. The variations are indicated in Table 1 by *slight*, *moderate* and *marked*, depending upon the degree and duration of convulsive seizures. Those rated *marked* lasted several minutes after the shock was applied and were accompanied by tonic and clonic contractions, frothing at the mouth, and involuntary defecation and micturition. *Moderate* convulsions were those which were quite marked during the application of the current but from which recovery occurred within a minute or two after the shock. *Slight* convulsions did not continue after the current was stopped.

TABLE 1.—TABULATION OF RESULTS.

Protocol No.	Dog.		Experiment.				Remarks.
	No.	Sex.	Duration, days.	No. of shocks.	Degree of severity of convulsions.	Recovery interval, days.	
1	1	F	25	14	Marked	0	
2	2	F	46	25	Marked	129	
3	3	M	31	17	Slight to moderate	26	
4	4	F	53	16	Moderate	4	
5	5	F	63	18	Marked	12	
6	6	M	53	15	Marked	42	
7	7	F	15	4	Marked	0	Killed for distemper
8	8	M	15	5	Marked	0	Very excitable
9	9	M	5	2	Marked	0	Death on 5th day (pneumonia)
10	10	M	15	5	Marked	0	Spontaneous death
11	11	F	26	8	Moderate to marked	0	Spontaneous death
12	12	F	14	5	Marked	1	

Many of the animals became quite unruly during the time the shocks were being given. A number of them even developed savage tendencies. On the other hand, dogs which were permitted to survive a number of weeks without the shock treatment did not exhibit any abnormal behavior during this recovery period.

* A paper is in preparation dealing with the brain changes in 2 human cases following electrical shock therapy.

† Manufactured by Rahm Instrument Company, 12 West Broadway, New York.

‡ Preliminary experiments showed that there was considerable variation in the susceptibility of dogs to the development of convulsions and that with a current of less than 80 volts, some of the animals failed to show convulsions at all.

Some of the animals in the series died during the experiment. The others were killed by bleeding, under nembutal anesthesia. Blocks of tissue from the various organs obtained at autopsy were fixed and prepared for histologic study by routine methods. Frontal sections were made of the brains and blocks were taken from frontal and temporoparietal cortices, basal nuclei, cerebellum, and medulla. These tissues were examined by the Nissl method; some of the tissues were prepared by the hematoxylin-eosin method and by the Loyez, Cajal, and Hortega methods.

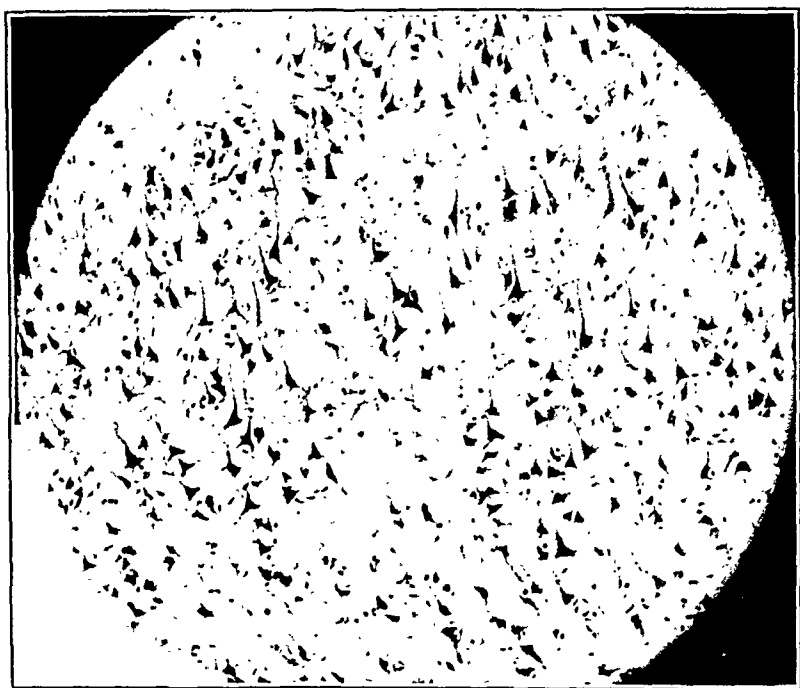


FIG. 1.—Small areas of cortical devastation from Dog 1 which had 14 marked convulsions. (Nissl, $\times 125$.)

Protocols. Dog 1. *Brain:* Changes marked. Vascular dilatation and petechiæ. Nerve cell changes: swelling, vacuolation, extrusion of nuclei, paleness. Some satellitosis and neuronophagia. Numerous scattered shrunken elongated dark cells without clearly visible nuclei. Occasional circumscribed areas of recent necrosis with severe and ischemic changes—little glial reaction. Edema in white matter; myelin sheaths swollen and kinked; no definite demyelination. Faintly basophilic grayish globules in white matter. Focus in subcortical white matter: small vein with round-cell infiltration, surrounded by dense area of proliferated oligodendro- and microglia. *Other organs:* Congestion.

Dog 2. *Brain:* Moderate number of swollen, vacuolated nerve cells with reticular cytoplasm. Occasional small areas of devastation, with ghost cells. Few glia stars at site of necrotic nerve cells. Slight swelling of macroglia; small numbers of fibrillary astrocytes. Swelling and kinking of occasional myelinated fibers; no definite demyelination. Small amounts of perivascular fat in white matter. *Other organs:* Congestion; slight acute pneumonitis.

Dog 3. *Brain:* In cortex and basal ganglia: swelling and vacuolation of numerous nerve cells; delicate network of strands and granules in cytoplasm of some. Nuclei generally well preserved. Numerous dark-stained

nerve cells. Occasional severe cell changes and ghost cells. Swelling of oligodendroglia in cortex. Changes disseminated, apparently independent of circulation. Moderately increased number of glia cells, especially microglia, in molecular layer of cerebellum. Purkinje cells well preserved. *Other organs:* Congestion.

Dog 4. *Brain:* Widely scattered nerve cells with swollen and vacuolated cytoplasm and normal nuclei. Few dark-stained elongated slender nerve cells. Many nerve cells normal. Rarely minute cortical foci with ghost cells; little or no glial reaction. Vascular dilatation and petechiæ in few cortical areas. Slightly increased amounts of perivascular fat in white matter. *Other organs:* Congestion; slight acute peribronchitis.

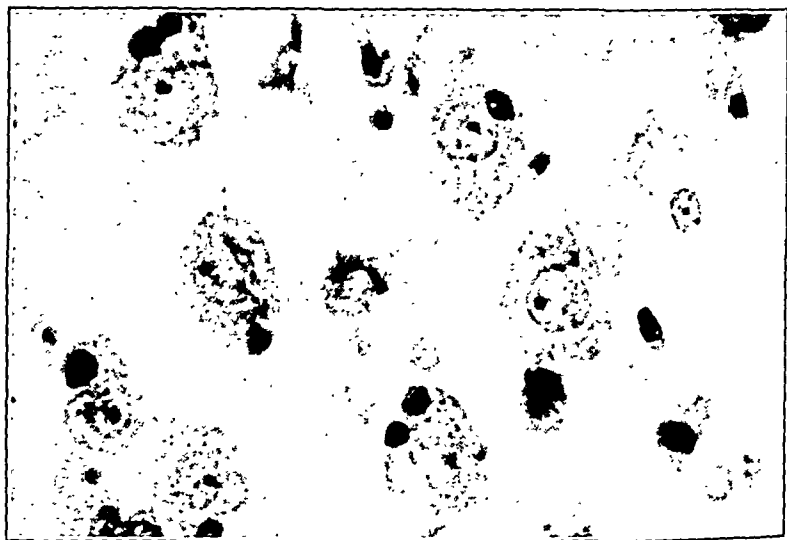


FIG. 2.—Swelling, granular appearance and vacuolation of cortical nerve cells from Dog 1 which had 14 marked convulsions. (Nissl, $\times 660$.)

Dog 5. *Brain:* Changes less pronounced than in others: some tigrolysis and vacuolation of nerve cells. Most nerve cells essentially normal. No glial reaction. Occasional vascular dilatation and petechiæ. Almost negligible swelling and diminished tingibility in myelinated fibers. *Other organs:* Congestion; diffuse acute pneumonitis; chronic pyelitis.

Dog 6. *Brain:* Swelling and vacuolation of many nerve cells; many cells normal. Occasional satellitosis and neuronophagia, especially in basal ganglia and thalami. Vascular dilatation and recent petechiæ in several parts of cortex. *Other organs:* Congestion.

Dog 7. No autopsy.

Dog 8. *Brain:* Changes in numerous nerve cells in all areas: swelling, vacuolation, indistinct cell borders, granular cytoplasm, occasionally intranuclear granules. Occasional severe changes and ghost cells. Little or no glial reaction. *Other organs:* Congestion.

Dog 9. *Brain:* Damage rather severe: tigrolysis, swelling, vacuolation, shrinkage, granular cytoplasm. Severe and ischemic cell changes. Nuclei more damaged than in others; many hyperchromatic and distorted. Glial reaction absent or slight; some early microglial proliferation in few areas. Marked congestion and occasional hemorrhage in meninges. Thickening

of ependymal lining; some subependymal gliosis and hemorrhage. Changes not those of autolysis. *Other organs:* Congestion; pneumonia with lung abscesses and empyema. (Severe pneumonic infection: animal had had only 2 electrical shocks.)

Dog 10.—No autopsy.

Dog 11. *Brain:* Dark-stained cells with "chronic" changes numerous. In some areas: paleness of cells, severe and ischemic changes. Glial reaction little or none. Many pyknotic nuclei. Few slightly swollen nuclei. Very rarely small "gliarosen." *Other organs:* Congestion; aspiration with slight patchy pneumonia.

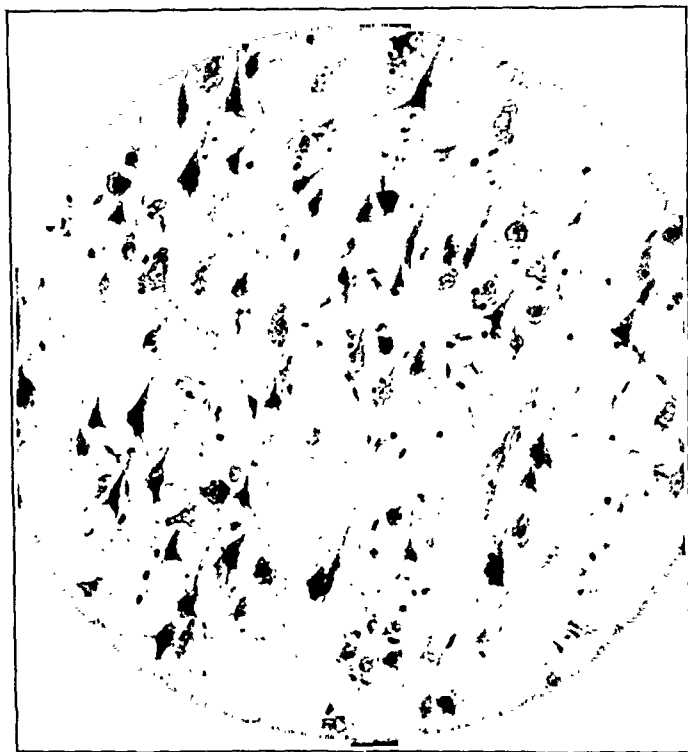


FIG. 3.—Sclerosed, ischemic, and granular cortical nerve cells from Dog 9 which had 2 marked convulsions. (Nissl, $\times 250$.)

Dog 12. *Brain:* Changes diffuse, somewhat similar to but less marked than those of Dog 9. Occasional minute foci: paleness and ghost nerve cells. Most glial nuclei small and dark; occasional large pale nuclei and "gliarosen." Few recent petechiae in meninges or near ependymal lining. *Other organs:* Congestion.

Results and Discussion. The most pronounced changes observed were in the brain. The cortex was more involved than the extra-cortical gray matter. The pathologic changes in the cortex were perhaps more noticeable in the vicinity of the pathway of the electrical current (temporoparietal cortex).

The following outstanding neuropathologic changes were observed. The nerve cells showed rather widespread damage, including tigrolysis, paleness, swelling, vacuolation, and in some instances

even ischemic and "severe" changes. Satellitosis and neuronophagia were found occasionally. In certain small circumscribed areas only pale, ischemic, ghostlike cells remained. Numerous cells exhibited "chronic" alterations: the cells appeared dark, slender and shrunken. The glia and microglia revealed slight proliferative changes. In a few of the animals some of the myelinated fibers showed slight damage, associated with a mild degree of edema in the white matter. The latter changes probably are of little significance. Vascular dilatation and minute hemorrhages were observed in the cortex, in the meninges, and around the ventricles in some of the brains. Congestion was the chief observation upon histologic examination of the other organs. The neuropathologic findings are similar in many respects to those of Morrison, Weeks, and Cobb,³ who found a tendency to hemorrhage, shrinkage of ganglion cells, mild reaction of glia, and absence of demyelination.

Although the changes described in the brain are definitely pathologic, they are not to be regarded as serious. Most of the nerve cell nuclei remained fairly well preserved. Many of the changes appeared to be reversible. The dogs during the recovery intervals failed to show clinical signs of brain involvement, as measured by the general behavior rather than by any specific neurologic tests. Variation in the degree of involvement may well be influenced by variation in individual susceptibility and by the degree of severity of the convulsions. In 2 dogs (Dogs 5 and 6), which had survived the experiments 12 and 42 days respectively, the findings were less pronounced than in the other dogs, although Dog 5 had 18 and Dog 6 had 15 markedly severe convulsions. On the other hand, Dog 2, which had undergone 25 markedly severe convulsions and was allowed to survive the experiment for 129 days, showed decided changes in the involved parenchyma. In 1 animal a small vein in the convolutional white matter showed lymphocytic infiltration and was surrounded by proliferated oligodendro- and microglia. Basophilic or grayish globules, observed only in the celloidin-embedded material, in the white matter of the same animal, are of questionable significance and possibly are artefacts. Similarly, the dark cells in the cortex may be artefacts, as recently pointed out by Scharrer.⁴

The investigations of several workers indicate that the brain changes induced by electrical shock are partly due to the direct effect of the current upon the brain parenchyma and partly due to the effect of the current upon the cerebral circulation (Morrison, Weeks, and Cobb, and Alexander¹). The fact that the changes tend to be slightly more severe in the vicinity of the pathway of the current suggests the possibility that the current exerts a direct action upon the brain parenchyma distinct from any effect upon the circulation. The findings of Morrison, Weeks and Cobb, as well as those of Echlin,² that the current brings about a contraction of the intracranial arteries, point to an involvement of the circulation in

the pathogenesis of the lesions. Petechiæ and small foci of ischemic necrosis observed in the present work also suggest circulatory effects.

For a long time it has been known that rather marked cerebral changes are to be found in patients with epilepsy. Recent use of convulsant therapy has renewed interest in the effects of convulsions upon the architecture of the brain. Shock therapy with insulin or metrazol has been shown to be accompanied by more or less marked pathologic changes in the brain.

Conclusions. The present studies indicate that some degree of neuropathologic change is to be expected in animals given electrical shocks of the same strength and duration as those employed clinically. Our results suggest that histologic changes induced by electrical shock in the brains of dogs are somewhat less severe than the changes we found following metrazol.⁵

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INTRAMUSCULAR PRESSURE.

III. THE ACTION OF VARIOUS DRUGS ON PATIENTS WITH NORMAL INTRAMUSCULAR AND VENOUS PRESSURE.*

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THE action of different drugs in various shock-like states wherein intramuscular and venous pressures fell to a low level, was reported in a previous communication.¹ It was observed that a 25% solution of Pyridine-beta-Carboxylic acid diethylamide (Coramine-Ciba) when administered intravenously raised the lowered level up to the normal range. Concomitantly, the low level of venous pressure

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was also raised. In shock-like states the range of increase in intramuscular pressure was from 19 to 65 mm. H₂O. The average increase in 14 observations was 38.5 mm. The range of increase in venous pressure was from 1.0 to 12.2 cm. H₂O. The average increase was 5.2 cm. (Table 1).

Our observations after the use of the drug on humans differed from those reported in animals² in two respects: 1, the marked pressor effect seen in animals was absent and, 2, there was a marked venous pressure increase in humans. The opposite observations were reported in normal animal experiments.

In an attempt to reconcile the discrepancy of these observations, Coramine, as well as other drugs which we also tested in shock-like conditions² was administered to ward patients who were either convalescing or otherwise not acutely ill. *The initial intramuscular and venous pressures of these patients were within the normal range of values at the outset of these experiments.* The difference in response to Coramine, between patients with low and normal levels at the outset is shown in Table 1.

TABLE 1.—DIFFERENCE IN RESPONSE TO CORAMINE BETWEEN PATIENTS WITH LOW AND WITH NORMAL LEVELS OF INTRAMUSCULAR AND VENOUS PRESSURE AT THE OUTSET.

	Mm. H ₂ O increase in intramuscular pressure.			Cm. H ₂ O increase in venous pressure.		
	Least.	Greatest.	Average.	Least.	Greatest.	Average.
In shock-like conditions wherein initial values are at a low level .	19	65	38.5	1.0	12.2	5.2
In normal subjects wherein initial values were within normal range	4	43	18.5	0.7	7.6	3.5

A17 and B25 (Exp. 1) had initial high intramuscular pressure levels; the others were within the normal range of 60 to 90 mm., noted by other workers.^{3*} The greatest increase in intramuscular pressure in normals, after Coramine was 43 mm., and the smallest was 4 mm., the average increase being 18.5 mm.† The increase in venous pressure was a maximum of 7.6 cm. and a minimum of 0.7 cm., the average increase being 3.5 cm. (Table 1). The pressor effect of Coramine was not constantly obtained. It was marked in the patient (A29) given 10 cc. of the drug intravenously (Exp. 1). In 2 apparently normal individuals, we failed to obtain the marked respiratory stimulation or increase of intramuscular pressure which characteristically follows the intravenous administration of 5 cc. of Coramine. The data on one such instance is shown in Experiment 2. In a previous communication we called attention to this discrepancy.

* We have noted values over 91 mm. and up to 116 mm. in 10 apparently normal individuals on 13 occasions. These were the highest values recorded by us in approximately 1000 intramuscular readings in 120 persons. The instruments described by Henderson³ was used in approximately 400 readings, and that by Gunther and Henstell⁴ was used in the remainder.

† The possible range of error in the measurement of intramuscular pressure is 10 mm. The possible error in venous pressure measurement in a quiet and co-operative patient is 1 cm.

One patient who was in shock likewise failed to show the characteristic respiratory response and an increase in a lowered intramuscular pressure following an initial dose of 5 cc. of Coramine intravenously.¹ However, the physiologic response followed administration of adequate amounts of the drug. The adequate dosage varied from 5 to 20 cc. With this exception noted, it was not necessary to administer more than 10 cc.

Coramine by mouth (10 cc.) showed no change in the intramuscular pressure (B25 Exp. 1).

TABLE 2.

Patient; Comments.	Time in minutes after injection.	Intramuscular pressure, mm. H ₂ O.	Venous pressure, cm. H ₂ O.	Blood pressure, mm. Hg.	Pulse rate per min.	CO ₂ , vols. %
<i>Experiment 1 on Coramine.</i>						
A17 Before		100	7.9			
Coramine 10 cc., intravenously	10	143	15.5			
	18	100	10.5			
A23 Before		69	7.6	120/80		
Coramine 5 cc., intravenously	2	85	10.0	122/84	105	
	7	79	8.3			
Then a second injection of Coramine 10 cc., intravenously	11	85	10.8	130/100	98	
	23	72	9.0	114/82	82	
A27 Before		93	9.7		72	
Coramine 10 cc., intravenously	4	113	15.3		125	
	10	91	10.8		88	
A29 Before		90	9.1	130/90		
Coramine 10 cc., intravenously	2	106	11.1	212/148		
	10	100	10.1	170/114		
	25	85	9.1			
B25 Before		110	7.2	112/70	76	
Coramine 10 cc., orally	10	114	7.5	110/76	76	
	20	110	7.9			
	30	109	6.6	104/72	68	
	50	107	6.5			
<i>Experiment 2 on Coramine, Atypical Response.</i>						
A23		75.3	7.6	118/82		
5 cc. Coramine I.V.*	2	87.3	8.7			
	11	82.5	8.4			
5 cc. Coramine I.V.*	3	14	91.3	10.0	122/84	
	10	24	84.5	8.3	122/84	
10 cc. Coramine I.V.*	26					
	5	31	90.5	8.8	130/100	
<i>Experiment 3 on Caffeine Sodium Benzoate.</i>						
A43 Before		66	5.7	148/95	88	
Caffeine Sodium Benzoate, 7½ gr., intravenously	5	66	6.8	175/110	100	
	15	66	7.2			
A53 Before		83	8.5	130/86	78	
Caffeine Sodium Benzoate, 4 gr., intravenously; then a second injection of 15 gr. intravenously	4	77	8.5	132/90		
	10	77	9.5			
		77	8.6	132/90	80	
	5	15	81	12.0	150/90	124
	10	20	77	11.5	150/88	124
A75 Before		98	8.8	95/72	60	
Caffeine Sodium Benzoate, 7½ gr., intravenously	7	103	11.8	120/90	56	
	12	98	9.9	116/82	56	
A94 Before		80	11.8	128/84		
Caffeine Sodium Benzoate, 7½ gr., intravenously	5	82	15.0	190/110		
	10	82	12.4			
A99 Before		87	5.1	126/76	80	
Caffeine Sodium Benzoate, 7½ gr., intravenously	5	85	9.2	165/120	100	
	10	83	5.1	165/98	84	
	15	73	4.7	142/96	76	
	25	72	4.9			

Patient; Comments.		Time in minutes after inhalation.	Intramus- cular pressure, mm. H ₂ O.	Venous pressure, cm. H ₂ O.	Blood pressure, mm. Hg.	Pulse rate per min.	CO ₂ , vols. %.
<i>Experiment 4 on Inhalation of CO₂ Gas.</i>							
A23	Before		74	8.1	120/76	80	
CO ₂ stopped		5	71	8.3			
		10	74	7.7	118/82	80	
A27	Before		80	7.3	145/95		
CO ₂ stopped		4	112	12.5	148/102		
		7	80	11.7	145/100		
		11	75	7.7			
A29	Before		96	9.1	124/90		46
CO ₂ stopped		5	114	10.6	130/90		48
		10	90	9.6			
A43	Before		58	7.2		92	58
		2	68	8.6			
CO ₂ stopped†		5	78	9.3	180/112	92	
		7	69	14.4			
		3	10	64	10.2	88	
		5	12	70	7.8		
		7	14	58	7.3		
		15	22	66	6.3	148/95	42
A75	Before		94	8.4			54
		1	100	9.8		70	
		3	103	10.1	94/70		
CO ₂ stopped		4	100	9.8			
		7	100	9.8			53
		2	9	100	8.5	56	
		5	12	92	7.6	80/60	
A89	Before		50	11.4	128/88	96	48
CO ₂ stopped		3	52	14.5	170/108	100	
		7	52	14.6			56
		2	9	50	10.2	100	
		8	15	44	9.7	126/90	96
		14	21	50	10.5	126/90	96

Experiment 5 on Voluntary Overbreathing.

		Time in minutes.					
A23	Before		73	7.5	120/80	80	
		3		9.6			
		4		9.1			
Overbreathing stopped		5	77	8.6	120/76	100	
		9					
		2	11	72	8.3		
		8	17	74	8.1		
A27	Before		87	9.8			
Overbreathing stopped		3	86	14.3			
Chvostek positive		7	86	14.3			
		22	29	80	9.9		
A29	Before		95	10.4	128/94		50
Overbreathing stopped		5	95	10.1			
		7					
		11	18	96	9.1	124/88	46
A43	Before		62	7.7	170/142	82	58
Chvostek positive		2	60	9.5		108	
Chvostek positive		4		8.7	175/115		
		5	49	8.7			
		7	41				48
Fagging out		8	52		162/106		
Chvostek positive		9	45	9.4	162/110		
		11	50	7.0			
Overbreathing stopped		12					
		3	15	6.0		88	
		13	25	45			
Chvostek positive		15	27	43	7.8	160/110	58
		32	44	67	6.7		
A75	Before		96	10.6	88/68	54	58
		2	97	13.1			
Chvostek positive		4	99	12.8			
Carpopedal spasm present		7	112	26.6	92/74	72	59
		10	165	26.6			
Overbreathing stopped		11	165	18.1			
		2	12	105	13.8		
Spasm gone		3	13	100	10.8	90/70	54
A89	Before		50	10.5	126/90	96	50
		3	50	10.8	142/90	100	
		5		12.0			46
Overbreathing stopped		7	64	14.0	150/100	120	
Chvostek positive		4	50	11.0	138/100	100	
Carpopedal spasm present		7		11.0	128/96	96	
		14	44	11.0	130/95	92	

Patient; Comments.	Time in minutes.	Intramus-	Venous	Blood	Pulse rate per min.	CO ₂ , vols. %.
		cular pressure, mm. H ₂ O.	pressure, cm. H ₂ O.	pressure, mm. Hg.		
Experiment 6 on Aminophyllin.						
B27	Before	100	7.1	102/56	68	
Aminophyllin, 7½ gr., intravenously	10		5.8	100/48	72	
	15	104	5.9	104/64		
	25	102	5.7	100/60	66	
	30	101	5.4			
B29	Before	84	14.4			
Aminophyllin, 7½ gr., intravenously	5	84				
	10	81	14.0			
	15	75	14.3			
	20	82	14.0			
Experiment 7 on Prostigmine.						
B27	Before	116	6.3	100/70	76	
Prostigmine 3 cc. of 1:2000 solution intramuscularly	5	109	6.8	100/64	68	
	10	103	7.0	90/58	68	
	20	109	7.8	100/62		
	30	100	7.4	102/56	66	
	60	100	7.1	102/56	68	
B29	Before	82	14.0			
1 cc. 1:2000 soln. intravenously 30 min. after 7½ gr. aminophyllin intravenously	5	81	13.7			
	10	80	13.9			
Then a second injection of 2 cc. 1:2000 solution intravenously	5	15	90	14.0	Twitching; muscle fibrillation	
	8	23	85	14.5		
	13	28	80	14.0		
	18	33	82	13.9		
	21	36	81	14.5		
Then atropine sulphate gr. 20, intravenously	5	41	82	14.6	Muscle twitching ceased	
	10	51	81	13.7		
Experiment 8 on Paredrine.						
B40	Before	74	7.2	120/70	84	
Paredrine 40 mg., subcutaneously	5	67	7.0	140/76	78	
	10	66	7.5	160/82	70	
	20	64	8.8	168/86	70	
	30	61	9.3	194/112	66	
	40	69	9.8	190/110	70	
	60	60	6.0	170/105	70	
	80	59	6.5	130/72	78	
B42	Before	88	9.2	120/70	80	
Paredrine 30 mg., subcutaneously	10	87	9.3	200/110	50	
	15	87	14.5	210/110	50	
	20	77	13.3	220/112	68	
	30	79	13.0	208/110	70	
	40	83	12.0	194/96	72	
	60	83	9.9	170/86	64	
	90	82	9.6	150/80	76	
B44	Before	76	8.0	132/90	60	
Paredrine 20 mg., subcutaneously	7	76	8.4	158/100	61	
	15	78	7.6	170/96	56	
	25	77	7.3	176/100	60	
	40	74	10.4	180/96		
	60	76	11.5	138/82		
B49	Before	87	9.3	125/92	59	
Paredrine 20 mg., intramuscularly	5	80	9.0	128/88	59	
	15	78	9.4	166/102	52	
	25	79	8.6	174/102	53	
	40	79	10.4	178/102		
	60	79	9.1	158/95	56	
	80	75	8.5	142/86	54	
B37	Before	112	12.6	120/80	80	
Paredrine 20 mg., subcutaneously	5	118	11.7	128/76	80	
	10	115	12.5	160/88	68	
	15	126	13.0	164/88	68	
	25	123	13.1	170/100	66	
	35	122	13.3	172/100	68	
	50	125	13.4	168/102	76	
	60	124	11.1	156/106	74	
	70	124	11.8	142/88	76	
	90	118	12.1	108/68	95	

Patient; Comments.		Time in minutes after injection.	Intramuscular pressure, mm. H ₂ O.	Venous pressure, cm. H ₂ O.	Blood pressure, mm. Hg.	Pulse rate per min.	CO ₂ , vols. %.
<i>Experiment 9 on Paredrinol.</i>							
B31	Before		105	7.8	128/90	94	
Paredrinol 25 mg., subcutaneously		5	105	7.8	136/100	92	
		10	105	8.3	142/92	96	
		15	102	8.3	154/88	81	
		20	103	8.0	162/92	80	
		25	104	8.4	164/98	80	
		35	104	8.0	148/92	80	
		45	100	8.3	142/98	84	
		60	95	8.0	124/88	84	
B39	Before		78	3.7	112/76	90	
Paredrinol 40 mg., subcutaneously		5	80	3.9	146/86	88	
		10	77	3.6	148/88	84	
		15	71	3.5	162/98	88	
		20	65	3.0	160/90	88	
		30	65	3.3	158/86	84	
		40	63	4.6	146/86	92	
		60	63	4.6	132/84		
<i>Experiment 10 on Strychnine Sulphate.</i>							
A99	Before		91	4.5	126/78	78	
Strychnine Sulphate $\frac{1}{10}$ gr. (I.M.), intramuscularly		5	92	4.5	126/76	80	
		10	94	4.0			
		15	85	4.1	124/72	72	
		20	81	4.4	124/72		
Then a second injection of $\frac{1}{20}$ gr., intramuscularly (I.M.)		10	30	5.7	128/76	78	
		20	50	5.2			
		30	80	5.1	126/76	80	
A103	Before		82	6.9	98/78	105	
Strychnine Sulphate $\frac{1}{10}$ gr. (I.M.), intramuscularly		7	84	6.6	102/78	104	
		12	80	6.7			
		17	80				
		20	74				
Then a second injection of $\frac{1}{20}$ gr., intramuscularly		30	77	7.9			
		5	35	8.1	96/78	106	
		10	45	7.9			
		15	60	8.2			
		20	80	9.0	102/78	104	
		40	120	7.9	98/76	104	
A107	Before		85	3.1	132/94	90	
Strychnine Sulphate $\frac{1}{10}$ gr. (I.M.), intramuscularly		10	87	3.6	134/92		
		20	82	3.6			
		25	81	3.5	130/90	110	
Then a second injection of gr. $\frac{1}{10}$, intravenously		30					
		5	35	3.6	132/92	96	
		25	55	4.1			
		65	95	3.4			

* No respiratory response.

† Patient protesting.

Caffeine sodium benzoate given intravenously to 5 normal patients (Exp. 3) showed no alteration in intramuscular pressure, whereas, there was a transitory increase in venous pressure paralleling the pressor effect.

Inhalations of carbon dioxide gas diluted in air by the drip method⁵ showed small but definite increases in intramuscular pressure and venous pressure (Exp. 4). These observations confirm those of Henderson *et al.*⁶ on normal individuals.

Overbreathing and blowing off the alveolar CO₂ (Exp. 5) showed no alterations in intramuscular pressure in 2 instances (A23 and A27) and a drop of intramuscular pressure 5 minutes after the experiment began in 1 instance (A43). Tetany was produced in 2 patients (A75 and A89) and an increase in both intramuscular and venous pressures was observed. In 2 patients (A27 and A43) in whom a Chvostek sign was the only indication of the overventilation, venous pressure changes alone were observed.

Aminophyllin given intravenously in 3 normal patients (Exp. 6) did not alter either intramuscular or venous pressure.

Prostigmine (Exp. 7) given to 1 normal patient intramuscularly did not alter either intramuscular or venous pressure.

Paredrine was given to 5 (Exp. 8) and Paredrinol to 2 normal individuals* (Exp. 9). No changes whatever were noted in intramuscular pressure up to 90 minutes. A transitory increase in venous pressure accompanied the pressor effect and is consistent with other recorded observations on these drugs.⁸

Strychnine (Exp. 10) was given 6 times to 3 normal patients in doses from gr. $\frac{1}{20}$ intramuscularly to gr. $\frac{1}{10}$ intravenously. No change was observed up to 40 minutes in either intramuscular, venous or blood pressures.

Discussion. The temporary venoconstriction and increase in venous pressure following the administration of pressor drugs such as Epinephrine or derivatives of Epinephrine is well known. An increase in venous pressure following the use of these pressor drugs is attributed to the indirect effect of an increase in blood pressure and to a direct constriction of the veins. Other factors on the effect of sympathicomimetic drugs and the mechanisms which cause a rise in venous pressure are thoroughly discussed by Iglauer and Altschule.⁸

The thesis has been proposed by Wells *et al.*⁹ that intramuscular pressure is directly due to and dependent upon venous pressure. The contrary view has been taken by Henderson,¹⁰ who has postulated the existence of a "venopressor" mechanism wherein the maintenance of venous pressure is to a large degree dependent upon intramuscular pressure, or as he prefers to term it, "muscle tonus."

The data presented here, as well as in our previous communications, show *an increase in venous pressure following the use of pressor drugs without an increase in intramuscular pressure*. Contrariwise *an increase in intramuscular pressure was always accompanied by a simultaneous and immediate increase in venous pressure*. This phenomenon is constant throughout our observations. In contrast, the increase in venous pressure, presumably by venoconstriction action *via* physiologic agencies as shown in (Exps. 3, 4 and 8) was not accompanied by an increase in intramuscular pressure. The most striking increases in intramuscular and venous pressures followed the intravenous administration of Coramine. The response in both of these when the intramuscular pressure was within the normal range at the outset was not of the magnitude observed when intramuscular and venous pressure readings were at low levels. The maximum responses of intramuscular and venous pressures is seen in postoperative depression and in shock-like conditions.¹ The failure to obtain an increase in venous pressure after the use of

* We are indebted to Dr. M. H. Nathanson for the Paredrine and Paredrinol used in these experiments. These data will also be used in another communication by Dr. Nathanson.⁷

Coramine in animals does not correspond with the observations in man.

Summary. Observations on the action of various drugs on intramuscular and venous pressures are shown in normal individuals. The drugs which are mainly pressor in action do not alter intramuscular pressure, whereas inhalations of CO₂ the tetanic state, and particularly the administration of Coramine intravenously definitely raise the level of intramuscular pressure. An increase in intramuscular pressure is accompanied by an increase in venous pressure, whereas the reverse was not observed.

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INTRAMUSCULAR PRESSURE.

IV. THE VENOPRESSOR MECHANISM DURING THE COURSE OF SURGICAL PROCEDURES.*

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INTRAMUSCULAR pressure drops to low levels in the early part of the postoperative period.¹ A low venous pressure was also observed within 6 hours after inhalational and 12 hours after spinal

* Aided by a grant from the Ciba Pharmaceutical Products, Inc., Lafayette Park, Summit, N. J.

Dr. Gunther is now in military service as Lieutenant-Commander, M. C., U. S. N. R., and Dr. Henstell as First Lieutenant, M. C., U. S. A. R.

anesthesia. In severe postoperative depression and in various shock-like states both intramuscular and venous pressure fell to low levels.² Restoration of intramuscular pressure to its normal level was accompanied by an immediate and striking increase in venous pressure, particularly after the administration of Coramine.² Venoconstrictor drugs, such as Paredrine, or physiologic activities such as overventilation without full tetany which increased venous pressure, did not affect intramuscular pressure; nor was the increase in venous pressure as prolonged or as great by these agents as that which occurred when the intramuscular pressure was increased by Coramine.³ This drug, related to the nicotinic acid fraction of the B vitamin* also acts as a venoconstrictor. The other factors which alter the level of venous pressure have been discussed by Igläuer and Altschule.⁵ Henderson's postulates of the venopressor mechanism⁴ are satisfied in the observations that (a) a low venous pressure and a low intramuscular pressure occur together in shock, and (b) a low venous pressure is markedly raised by an increase in intramuscular pressure, and (c) venous filling and clinical improvement in shock-like states appears after the use of an intramuscular pressor drug such as Coramine.

Problem. Does the converse of these observations hold true? Is a fall in intramuscular pressure immediately followed by a fall in venous pressure? Where, during the course of operation does the depression in vitality and/or the fall in intramuscular pressure occur?

Method. The apparatus described by Gunther and Henstell⁶ permitted the rapid and repeated simultaneous readings of intramuscular and venous pressures without interfering with the sterile technique of operative procedures. Observations were made on 10 patients; 4 during the entire course of the surgical procedure; 5 before and immediately following operation; 1 wherein the patient entered into shock during the course of a pericardial thoracentesis.

Results. The earliest drop in intramuscular pressure (a drop over 10 mm. H₂O) during the course of surgery was detected 50 minutes after the beginning of the operation and 60 minutes after the anesthesia was begun. The extremes of the initial drop in intramuscular pressure varied from 10 to 65 mm. H₂O and values over 16 mm. H₂O were associated with a drop in venous pressure of from 2.9 to 6.9 cm. H₂O.

After its initial fall, intramuscular pressure continued to drop and reached its maximum low level within the extremes of from 50 minutes to 20 hours. Seven of the 8 operative patients showed the maximum drop in 12 hours or less, confirming our previous observations.¹

The earliest change in venous pressure during surgery occurred 50 minutes after the beginning of the operation (Fig. 1). In 4 out

* Coramine is a 25% solution of Pyridine-beta-carboxylic acid diethylamide.

of 7 instances, the drop in venous pressure was concomitant with the initial fall in intramuscular pressure, and in 3 patients the intramuscular pressure fell first, the venous pressure later.

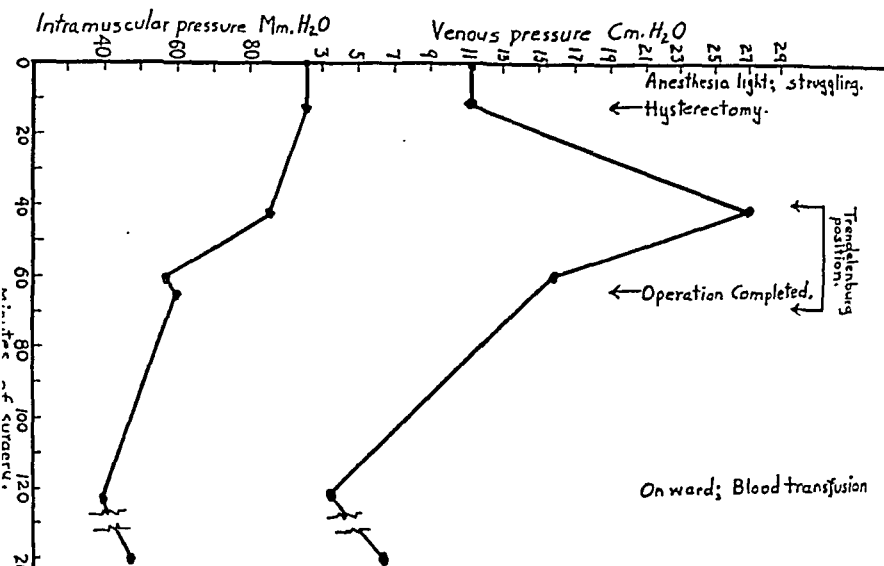


FIG. 1.—Hysterectomy. Fall in intramuscular pressure during surgery, preceding the drop in venous pressure. The maximum fall in venous pressure occurred 2 hours after the beginning of the operation and coincided with the moment of maximum drop in the intramuscular pressure.

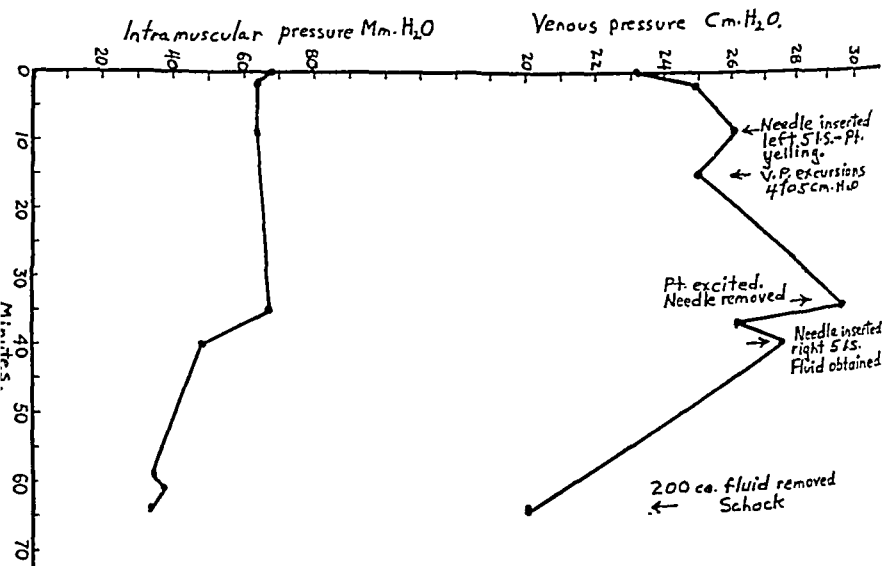


FIG. 2.—Pericardial thoracentesis for patient with pericardial effusion and heart failure. Intramuscular pressure dropped within 5 minutes after the pericardium was pierced. A shock-like state appeared promptly which was pronounced 20 minutes later when the maximum fall in venous pressure appeared.

TABLE 1.

Patient.	Type of operation.	Duration of operation.	Initial drop in intramuscular pressure in mm. H ₂ O.	Duration of operation when initial drop in intramuscular pressure occurred.	Initial drop in venous pressure in cm. H ₂ O.	Time interval after initial fall of intramuscular and venous pressure, when maximum fall in intramuscular and venous pressures occurred.	Total duration of time from beginning of operation.	Maximum drop in intramuscular pressure in mm. H ₂ O.	Maximum drop in venous pressure in cm. H ₂ O.
A41	Pericardial thoracentesis	20 min.	19	5 min.	0	20 min.	25 min.	36.0	3.0
A21	Cholecystectomy	63 min.	20	50 min.	4.7	12 hrs. 10 min.	13 hrs. 8 min.	51.0	12.0
A12*	Radical mastectomy	1 hr. 22 min.	16	60 min.	0	10 min.	70 min.	20.0	1.0*
A7	Supravaginal hysterectomy	2 hrs.	39	60 min.	0	1 hr. 7 min.	2 hrs. 7 min.	56.0	7.7
A1	Fusion of lumbar spine	2 hrs. 13 min.	16	81 min.	2.9	8 hrs. 39 min.	10 hrs.	35.0	11.9
A69	Cholecystectomy	3 hrs.	65	2½ hrs.	6.9	50 min.	3 hrs. 20 min.	64.0	7.9
A49	Encephalogram	2½ hrs.	22	2½ hrs.	0.9	7 hrs.	9½ hrs.	20.0	3.1
A57	Exploration of cervical cord	4 hrs.	22	Not recorded until 4 hrs.	0	20 hrs.	24 hrs.	22.0	3.2
A84	Nephropexy†	50 min.	10†	Not recorded until 9 hrs.	Not recorded	...	9 hrs.	10.0	0.0†
A61	Nephropexy†	55 min.	9†	Not recorded until 5 hrs. 10 min.	0	...	5 hrs. 20 min.	10.0	0.0†

* Variations and allowable error in venous pressure, 1 cm. H₂O.† Variations and allowable error in intramuscular pressure, 10 mm. H₂O.

In all patients, however, in whom intramuscular pressure had been low for 50 minutes or longer, a maximum fall in venous pressure occurred. This coincided with the time of the maximum fall in the intramuscular pressure. The maximum drop in intramuscular pressure varied from 20 to 64 mm. H₂O and the venous pressure from 3.2 to 12.2 cm. H₂O (Table 1).

In 2 instances in which the change in intramuscular pressure was 10 mm. or under, no alteration occurred in the venous pressure* (Fig. 2).

During the course of the pericardial thoracentesis intramuscular pressure was found at a low level within 5 minutes after the pericardium was pierced, and a deep state of depression and a fall in venous pressure occurred within 20 minutes. This was the earliest change in the venous pressure observed by us. The venous pressure dropped 3 cm. below the initial preoperative level, and 95 cm. below the highest value obtained during the thoracentesis (Fig. 2).†

The types of operation were encephalogram, cord tumor, fusion of the spine, radical mastectomy, nephropexy, hysterectomy, cholecystectomy, and pericardial thoracentesis.

The least changes in the venopressor mechanism occurred during a hysterectomy, and a radical mastectomy (Fig. 3.) The intramuscular pressure fell 25 and 16 mm. H₂O respectively and the venous pressure but 1 cm. H₂O.‡ The greatest changes were during cholecystectomy, which showed a fall of 64 mm. H₂O in intramuscular pressure and 7.9 cm. H₂O in venous pressure. In contrast to the first case, a second instance of hysterectomy showed a fall of 56 mm. H₂O in intramuscular pressure and 7.7 cm. H₂O in venous pressure.

Discussion. Intramuscular pressure begins to drop in surgical procedures of 50 minutes or longer duration. A simultaneous fall in venous pressure was observed in half the cases and in half of the observations a fall in intramuscular pressure preceded the drop in venous pressure. Furthermore when the intramuscular pressure remained low or continued to drop for a period of 50 minutes or more, the venous pressure also continued to fall and showed its maximum drop at the time when the intramuscular pressure was at its lowest level. The speed with which postoperative depressions occur is due to factors which do not lend themselves to analysis by these measurements. The 4 patients studied during the course of surgery, as well as in the period of postoperative depression, all

* The error of the method on consecutive readings is a range of 1 cm.

† It is appreciated that the fall in venous pressure might be due to the withdrawal of pericardial fluid. However, the drop in venous pressure which occurred after a fall in intramuscular pressure had taken place, is strikingly parallel to the phenomena observed in postoperative depression, and in other shock-like states, wherein a similar fall in venous pressure occurs after the intramuscular pressure drops. This is seen in patients who are in shock-like states and not in heart failure. The decrease in venous pressure cannot be attributed to a withdrawal of pericardial fluid.

‡ The range of variation and error allowed in any series of venous pressure measurements is 1 cm.

showed an initial fall in intramuscular and venous pressure after 50 minutes of surgery and a further decrease in these values in from 50 minutes to 12 hours. The patient who entered into a shock-like

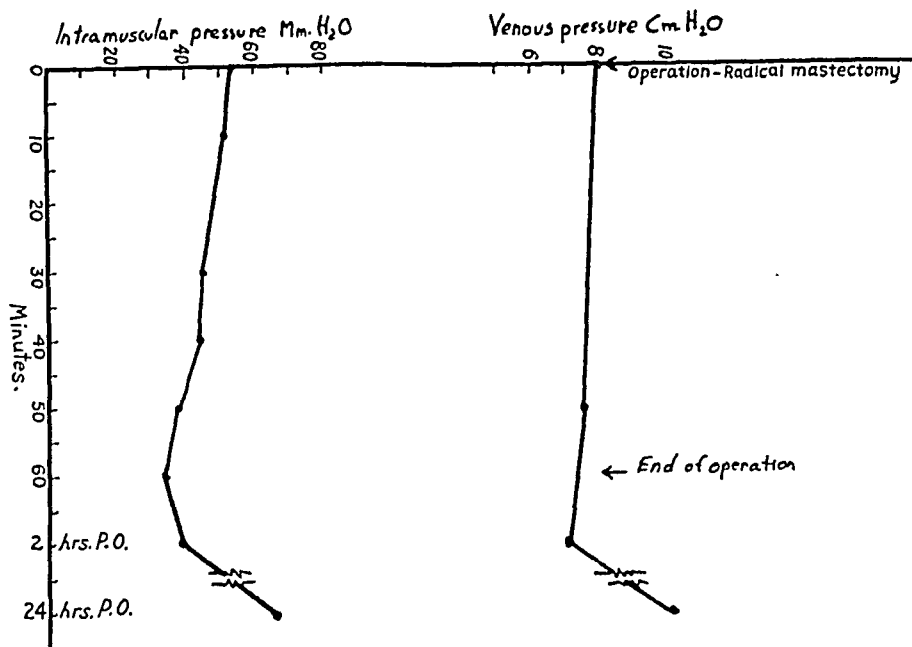


FIG. 3.—Radical mastectomy. Gradual decrease in intramuscular pressure after 40 minutes and outside the limit of error of the method of measurement after 50 minutes. Spontaneous recovery of intramuscular pressure, within limit of error of measurement, 2 hours postoperatively. The venous pressure measured 2 hours postoperatively had dropped only 1 cm. likewise just within the limit of error of measurement.

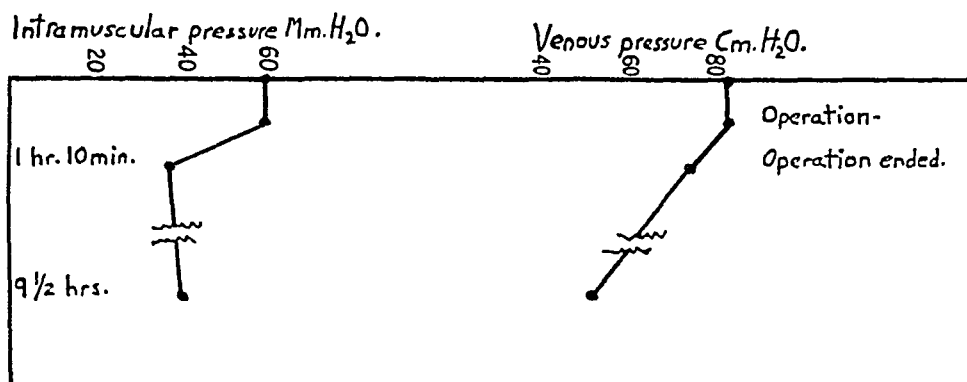


FIG. 4.—Showing the typical findings, summarized, of the course of surgical procedures. Operation, encephalogram. Intramuscular pressure begins to drop after 50 minutes, or in the neighborhood of 1 hour, precedes the fall of venous pressure, and both show their maximum drop concomitantly.

state during pericardial thoracentesis did so with great rapidity, and his intramuscular pressure dropped within 5 minutes and venous pressure within 20 minutes after the pericardium was

pierced. The occurrence of a drop in intramuscular pressure corresponds closely to the moment when vitality begins to ebb, as evaluated by the clinical eye.*

Conversely, as we pointed out before,^{1,2} a return of intramuscular pressure values to normal coincided with the spontaneous recovery in the uncomplicated postoperative course. Contrariwise, the patients who entered into shock postoperatively did not recover intramuscular pressure. It remained at a low level throughout the period of the postoperative depression and into the shock-like state. At this juncture of the clinical picture, when the intramuscular pressure was at its lowest level, the veins were collapsed and needles were inserted with difficulty. An induced restoration of intramuscular pressure, by the use of Coramine, restored venous pressure, resulted in venous filling and coincided with rapid though not permanent clinical improvement.

Summary. In 4 patients studied during the course of operative procedure under inhalational anesthesia, intramuscular and venous pressures dropped after 50 minutes of surgery. Within 50 minutes to 12 hours after the initial fall, the maximum decrease occurred in both intramuscular and venous pressures. In 2 patients studied during the course of operative procedure, the fall in intramuscular pressure preceded the decrease in venous pressure by 1 to 12 hours. In 1 patient with congestive heart failure undergoing pericardial thoracentesis, the fall in intramuscular pressure preceded the drop in venous pressure by 20 minutes and occurred within 5 minutes after the pericardium was pierced—after which time the patient rapidly entered into a shock-like state. Two patients observed within 9 hours after nephropexy whose intramuscular pressure change was 10 mm. showed no alteration in venous pressure.

Conclusions. 1. After 50 minutes of continuous surgery a drop in intramuscular pressure may precede the fall in venous pressure. In half the instances the low level of venous pressure coincided with the initial drop in intramuscular pressure.

2. When intramuscular pressure falls and remains low for 50 minutes or longer, a further decrease in venous pressure occurs which reaches its maximum low point concomitantly with the maximum drop in intramuscular pressure.

3. Intramuscular pressure fell 5 minutes before the shock-like state began and the venous pressure with its full appearance 20 minutes later during a pericardial thoracentesis, and

4. Further evidence is presented which supports Henderson's postulate in that: (a) intramuscular pressure first fails in shock-like states, and (b) with the failure of intramuscular pressure appears a failure in the maintenance of venous pressure and flow.

* Shock is defined by Webster's new International Dictionary, 2d ed., unabridged, Springfield, Mass., G. & C. Merriam Company, 1941: "A state of profound depression of the vital processes of the body . . ."

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THE ACTION OF STEROID COMPOUNDS ON THE VAGINAL EPITHELIUM OF THE RAT.

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CORNIFICATION of the vaginal epithelium is generally thought to be the most specific indicator of "estrogenic" or folliculoid activity, while mucification of the epithelium is regarded as a sign of a "corpus luteum hormone-like" or luteoid effect. Although the estrane derivatives are the outstanding representatives of that group of steroids exhibiting primarily folliculoid actions, a few "exceptional" androstane or *allo*-pregnane derivatives have been reported as showing to some extent this type of activity. With regard to these latter compounds the literature is highly confusing since in most instances the vaginal cornification observed by some workers could not be reproduced by others. For testosterone and ethinyl testosterone it has been shown (1) that the reason for this disagreement lies in the fact that the vagina of spayed rats treated with these steroids undergoes a transitory cornification followed by mucification. Noble¹ observed a transitory appearance of cornified cells in the vaginal smears of testosterone treated rats, but concluded that the significance of the "estrus response is probably doubtful and may be related to the collection of epidermal debris which occurs, especially in view of the fact that the clitoris region undergoes extensive cornification." However, our above-mentioned findings, obtained by examination of histologic sections through the vagina, proved

* This work was done under the tenure of the Aletta Marty Memorial Scholarship awarded by the Queen's Alumnae Association.

that this interpretation is incorrect and that a true transitory cornification occurs. On the other hand, it should be emphasized that conversely typical folliculoids, such as estradiol or estrone, may cause mucification instead of the usual cornification if they are administered in subthreshold doses. Hence it has been concluded that mucification and cornification are closely allied phenomena produced by a number of steroids but that neither one nor the other type of reaction is absolutely specific for any one compound.² These investigations appear to indicate that the type of vaginal reaction—cornification or mucification—is dependent upon a variety of factors influencing the responsiveness of the epithelium and not merely upon the chemical structure of the compound given. In the light of these findings vaginal cornification and mucification are not as specific of folliculoid and luteoid activity, respectively, as has previously been thought. The responsiveness of the vaginal epithelium is of great value, however, in spotting hormonally active steroids, since it was found that stratification of the vaginal epithelium, with or without cornification or mucification of the surface layer, is a pharmacologic action common to all hormonally active steroids.²

The object of the present communication is to report upon the vaginal effect of 49 steroids. On the basis of these studies an effort is made to correlate the chemical structure of these compounds with their effect on the vagina.

Experimental. All steroids were administered either in true solution or in fine crystalline suspension depending on their solubility. The relevant experimental details are mentioned in the following two tables which are almost self-explanatory. Table 1 summarizes our observations on ovariectomized rats receiving the different compounds subcutaneously twice daily in 0.1 ml. of peanut oil. Table 2 contains the results of acute experiments in which the steroids were administered by a single intraperitoneal injection in peanut oil to partially hepatectomized immature rats weighing 40 to 60 gm. (average 44 gm.). This second series was originally performed for the study of the anesthetic effect of steroids and it is for this reason that sensitization by partial hepatectomy and the intraperitoneal route of administration were chosen. However, since in all cases histologic sections of the vagina have been examined, the material is quite satisfactory for the problem under consideration in this study. For the details of the technique of hepatectomy and the acute hormone overdosage, as practised in this second series, the reader is referred to the paper of Selye.² The full systematic name of each steroid is given in order to avoid confusion. Underneath the common name appears in block letters in those cases in which the compound is generally referred to by a popular name. The melting point of the sample available to us was determined in our laboratory and is given in the table as an indicator of the degree of purity of the sample and also because it facilitates identification of the compound wherever there is doubt about several possible isomerids. If only small amounts of a steroid were available the number of animals used was necessarily small and treatment had to be short. Hence many of these, not readily obtainable substances, could be tested only in acute experiments. All these details, as well as the body weight of the experimental animals, are recorded in our

tables. The state of the vaginal epithelium, as indicated by histologic examination of paraffin embedded hematoxylin-eosin stained sections, is described in the last 3 columns of the tables under the subheadings of stratification, cornification and mucification. The degree of each of these changes noted is expressed in terms of an arbitrary scale ranging from 0 to 3. 0 means identical with untreated controls, 1(?) is a questionable effect, 1 a definite but very slight effect, 2 a marked effect and 3 the greatest change observed. These numbers represent average readings in which all animals of a certain group are taken into account. Whenever some animals in a group responded differently from the rest, a figure in brackets indicates the number of animals in the group which responded in this particular fashion. For instance in the case of the first compound of Table 1 the reading: "stratification 3, cornification 3(1), mucification 0" means that maximal stratification was seen in all animals of the group, but only a single animal showed maximal cornification, while none exhibited any trace of mucification. Wherever the available evidence convinced us that a compound has a definite vagina stimulating effect of any type, the figures in the table are given in block letters.

The most striking fact which emerges from a study of our tables is that all hormonally active steroids cause some degree of vaginal cornification in the spayed or immature rat irrespective of their main pharmacologic action. The great majority of the compounds examined cause only transitory cornification followed by mucification. Apart from the active estrane derivatives—which have not been included in our tables—only Δ^5 -androstenediol (Cpd. 4), dehydro-*iso*-androsterone (Cpd. 5), its acetate (Cpd. 6) and pregnenolone (Cpd. 14) maintained the vagina continually cornified. With all other compounds mentioned the phase of cornification was followed by mucification. In many instances parts of the vagina were mucified while other regions showed definite cornification.

Only little can be said about the correlation between chemical structure and vaginal effect. As shown by the above-mentioned examples of compounds 4, 5, 6 and 14, both androstane and 17-ethyl androstane derivatives can imitate the estrane derivatives in causing continuous vaginal cornification. However, this is not true of the great majority of the active compounds which cause only transitory cornification followed, or accompanied, by mucification. On the basis of these observations it appears necessary to reexamine many of the steroids whose "folliculoid" effect has been postulated merely on the basis of short-term vaginal smear tests.

The presence of a hydrogen at C₅ in a position *cis* to the C₁₀ methyl group (as in etiocholane and pregnane derivatives) invariably interferes with the vagina stimulating action of the steroids. This is in agreement with the more general concept (2) that such compounds are devoid of any known hormonal action although they may be very potent with regard to their anesthetic effect.

A five-membered ring D is not essential for the vagina stimulating action as shown by the two isomeric chrysopregnene derivatives (Cpds. 28 and 29) in which ring D is six-membered. Compounds having a long side chain at C₁₇ proved inactive but this may be due

TABLE 2.—EFFECT OF ACUTE TREATMENT WITH VARIOUS STEROIDS ON THE VAGINAL EPITHELIUM.

No. of Cpd.	Steroid.	M.P., °C.	No. of animals.	Dose in mg.	No. of hours between time of injection and death.	State of vaginal epithelium as indicated by histologic section.		
						Stratifica- tion.	Cornifica- tion.	Mucifica- tion.
30	Androstane-3,17-dione	132-134	3	10	12-24	0	0	0
31	6(α)-acetoxy- Δ^4 -androstene-3,17-dione		1	5	6	3	0	0
32	17-ethyl-androstane. <i>Allo-pregnane</i>		2	20	24	2	0	0
33	17-ethyl-androstane-3,17-diol-20-one-diacetate.	81-82.5 172	1	5	24	1(?)	0	0
	<i>Reichstein's CPD. "L"-diacetate</i>							
	17-ethyl- Δ^4 -androstene-17,21-diol-3,11,20-trione.	215-218	1	5	18	2	0	0
34	17-ethyl- Δ^4 -androstene-3-one-17(α)-ol. <i>Kendall's CPD. "E"</i>	139	3	5	18	1(?)	0	0
35	17-vinyl- Δ^4 -androstene-3-one-17(α)-ol. <i>17-Vinyl-testosterone</i>	139 139 139	4 1 3	10 25 5	18 14 18	1(?) 1 2	0 0 0	0 0 0
		184-187	3	10	18	2	0	0
		184-187	4	25	14	0	0	0
		184-187	1	20	24	0	0	0
		108-109	4	20	30	0	0	0
		125-127	4	20	24	0	0	0
		149	6	20	24	0	0	0
36	17-vinyl- Δ^4 -androstene-3(β)-17(?)-diol. <i>17-Vinyl-androstenediol</i>	175-177 205-207	2 3	20 20	24 24	0 0	0 0	0 0
37	<i>Cholestane-3(β)-6(β)-diol-diacetate</i>	196-198	2	20	24	0	0	0
38	<i>6-Keto-cholestanol-3(β)-acetate</i>	162-174	2	20	24	0	0	0
39	<i>Cholesterol</i>	151-153	3	10	18	0	0	0
40	<i>Cholesterol-half-succinate</i>	271	1	10	18	0	0	0
41	<i>Diosgenin acetate</i>	271	1	20	24	1(?)	0	0
42	<i>Diosgenin</i>	141-143	2	20	24	0	0	0
43	<i>Pseudodiosgenin</i>	198-200	2	20	24	0	0	0
44	<i>Etiocholane-3(β)-ol-17-one</i>	144-146	3	20	26	0	0	0
45	<i>Sodium-17-ethyl-etiocholane-3(α),20(α)-diol-glucuron- idate. Na-pregnandiol-glucuronidate</i>	164-170	3	20	24	0	0	0
46	17-ethyl- Δ^4 -etiocholone-3(β)-ol-20-one-acetate		1	20	24	0	0	0
47	<i>Sarsapogenin</i>		1	20	24	0	0	0
48	<i>Sarsapogenin acetate</i>		3	20	26	0	0	0
49	<i>Sarsapogenin</i>		3	20	24	0	0	0
	<i>Pseudosarsapogenin</i>		3	20	24	0	0	0

to the fact that all the long side chain compounds available to us had no oxygen in the immediate vicinity of the C_{17} pole of the molecule. 21-ethyl-progesterone (Cpd. 19) indicates that at least a butyl side chain at C_{17} is not incompatible with hormonal activity as long as there is an oxygen at C_{20} in the immediate vicinity of the

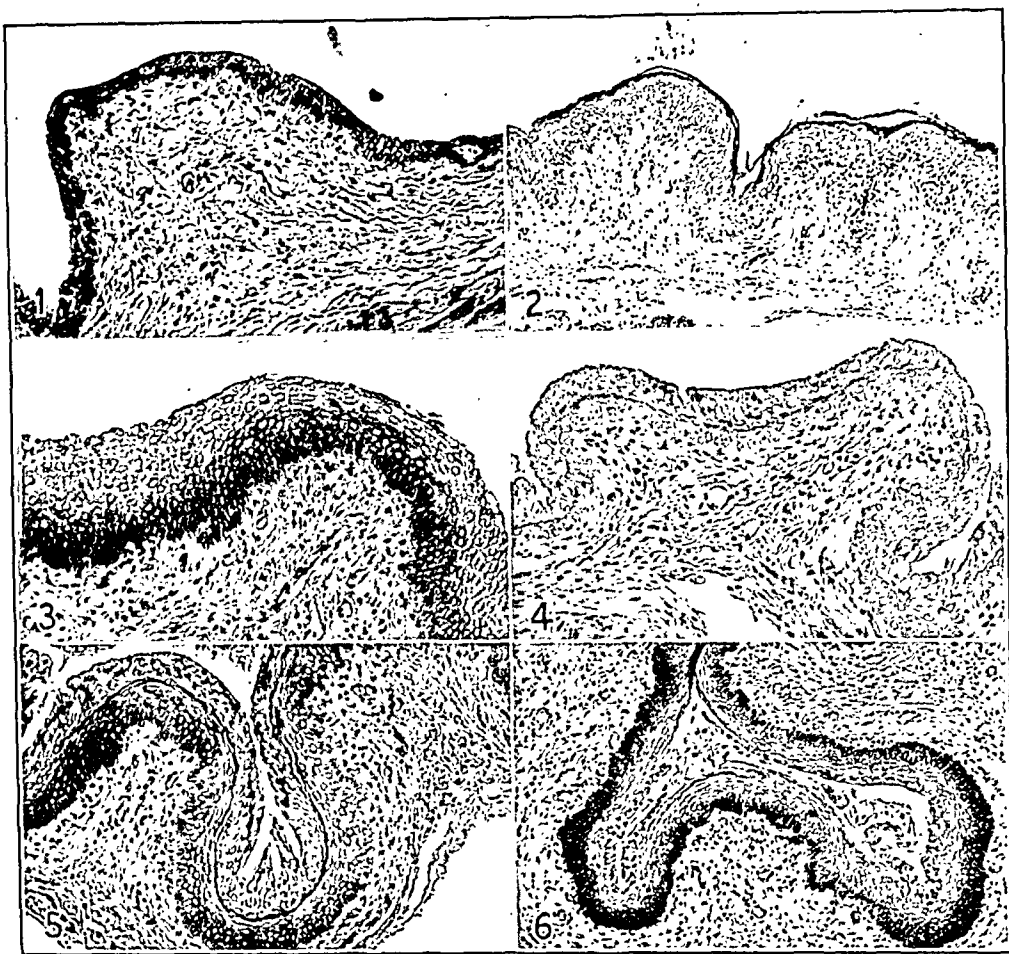


FIG. 1.—Vaginal epithelium of untreated immature rat. Cells are irregular in shape and form only 2 to 3 layers.

FIG. 2.—Vaginal epithelium of immature rat 24 hours after the intraperitoneal injection of 5 mg. of progesterone. Note the high stratified squamous epithelium with the formation of cornified scales on the surface.

FIG. 3.—Vaginal epithelium of immature rat 24 hours after the intraperitoneal administration of 5 mg. of α -estradiol. Note the high squamous epithelium which at this time shows no signs of cornification.

FIG. 4.—Vaginal epithelium of immature rat which received the same treatment as that shown in Figure 3. In this instance the surface layers underwent mucification. It should be noted, however, that judged by other experiments, in both these cases cornification would have ensued if estradiol treatment had been prolonged.

FIG. 5.—Vagina of immature rat given an intraperitoneal injection of 10 mg. of acetoxypregnenolone (Cpd. 15). Note definite layer of cornified cells underneath the surface stratum of mucified cells.

FIG. 6.—Vagina of an immature rat which received the same treatment as that shown in Figure 5. The epithelium at the depths of the crypts is mucified and at the peaks of the ridges cornified.

side chain attachment. We were surprised to note that *allo*-pregnane caused moderate but definite vaginal stratification since this appears to indicate that oxygen-free parent hydrocarbons may also exert hormonal actions. However, the amount of this compound available to us was sufficient for 2 rats only and hence we do not feel justified to draw the important conclusion that oxygen-free molecules can cause vaginal cornification.

It appeared of interest to us that many of the compounds which we examined simultaneously caused cornification in one area and mucification in another region of the vagina. Frequently the top layers of the epithelium were mucified, while the deeper layers showed definite cornification (see Fig. 5). In other instances the depths of the vaginal crypts were mucified, while the more exposed ridges showed cornification (see Fig. 6). These observations and the well-known fact that repeated local injuries to the vaginal epithelium may cause cornification even in spayed rodents appear to support the concept that incidental local factors may determine the type of vaginal response caused by a steroid of a certain chemical structure. In order to test this hypothesis we performed an experiment on 6 spayed albino rats (weighing 122 to 156 gm.) in which the vagina was mechanically distended by filling it with small glass beads and occluding the vulvar orifice with a purse-string suture. These animals as well as 6 spayed controls (132 to 158 gm.) were then treated with 5 daily subcutaneous injections of 5 mg. of progesterone dissolved in 2.5 ml. of peanut oil. On the day following the last injection the animals were killed and their vaginas sectioned. While the controls showed vaginal mucification, the animals whose vaginas had been distended exhibited marked stratification and cornification, under the influence of progesterone treatment. It is true that partial or transitory cornification occurs even in otherwise untreated progesterone injected animals (see Fig. 2) but this is invariably accompanied or followed by mucification. In the present experiment mechanical distention of the vagina completely inhibited mucification in the case of all animals, thus indicating that local factors are of the utmost importance in determining the type of vaginal response to a prevaillingly mucifying steroid such as progesterone. The fact that even active estrane derivatives may cause vaginal mucification under certain experimental conditions has been mentioned previously in this paper (see Fig. 4). Prior to cornification of the surface layers such compounds may cause the development of a stratified squamous, but not cornified, epithelium (see Fig. 3). Thus it is evident that all known hormonally active steroids (folliculoids, luteoids, corticoids, testoids) which have been tested, stimulate the development of the vaginal epithelium and may, depending upon the conditions of the experiment, cause mere stratification, stratification with cornification, or stratification with mucification.

Summary and Conclusions. A study of the vaginal effect of 49 steroid compounds on ovariectomized or immature rats reveals that all hormonally active steroids (folliculoids, luteoids, corticoids, testoids) stimulate the vaginal epithelium to undergo stratification, cornification and mucification. While cornification is the most common type of response to estrane derivatives, mucification is more frequently seen following treatment with androstane and 17-substituted androstane derivatives; but even the latter compounds elicit at least transitory cornification. All etiocholane and 17-substituted etiocholane derivatives proved inactive unless the C₅ hydrogen was removed by the presence of a Δ^4 or Δ^5 double bond.

Local factors play an important part in determining the histologic type of vaginal response caused by a certain steroid. Thus mechanical distention of the vaginal walls causes a dose of progesterone, which normally elicits mucification, to produce cornification.

On the basis of our observations we are inclined to believe that incidental factors determine the type of the vaginal response to steroid compounds but that some type of proliferation of the surface epithelium is an action common to all steroid hormones.

ACKNOWLEDGMENTS: The expenses of this investigation were defrayed by a grant from the Blanche E. Hutchinson Fund of McGill University. The authors are particularly indebted to the following chemists who supplied the steroids without which this investigation could not have been performed: Professors L. Ruzicka (University of Zürich, Switzerland), L. Fieser (Harvard University), R. D. H. Heard (Dalhousie University), T. Reichstein (University of Basel, Switzerland), E. C. Kendall (Mayo Clinic), J. S. L. Browne and E. Venning (Royal Victoria Hospital, Montreal), M. Ehrenstein (University of Pennsylvania) and Drs. C. Scholz (Ciba Company, New Jersey), E. Schwenk (Schering Corporation, New Jersey), O. Kamm (Parke, Davis & Company, Detroit), A. D. Odell (Charles E. Frosst and Company, Montreal), O. Wintersteiner and H. E. Staveland (Squibb Institute), D. Beall and A. S. Cook (Ayerst, McKenna and Harrison, Ltd., Montreal).

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TREATMENT OF ACUTE OPIUM POISONING. BENEFICIAL EFFECT OF CORAMINE.

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IN marked contrast to the rarity of poisoning with opium and its derivatives in America¹ and Europe² is the experience in the Peiping

* We understand that the P. U. M. C. has been discontinued by military order and that at least one of the authors is in custody.—EDITORS.

Union Medical College Hospital where patients with acute opium poisoning belong to the most frequent emergency cases. For the last 10 years the number of our patients with opium poisoning has steadily increased and lately it has reached remarkable dimensions (Table 1).

TABLE 1.—NUMBER OF CASES OF OPIUM POISONING ADMITTED.

Period.	No. of cases of opium poisoning.
July 1, 1930-June 30, 1931	14
" 1931- " 1932	25
" 1932- " 1933	41
" 1933- " 1934	26
" 1934- " 1935	44
" 1935- " 1936	42
" 1936- " 1937	48
" 1937- " 1938	62
" 1938- " 1939	98
" 1939- " 1940	103
April, 1941-Nov. 4, 1941	141

Fortunately *early* intervention in the form of gastric lavage with diluted KMnO_4 solution ($\frac{1}{5000}$) saves the lives of most of these patients, especially if the amounts of opium taken are not too large. If coma can be prevented by this or other measures, danger usually does not exist. In 1938 to 1939 no patient with opium poisoning without coma died. In 1939 to 1940 only 2 such patients died without coma.

TABLE 2.—MORTALITY OF COMA DUE TO ACUTE OPIUM POISONING BETWEEN 1930 AND 1940.

Year.	Total number of opium poisoning.	Total number of coma cases.	Deaths.	Mortality of coma cases.
1930-1940	503	169	120	71.0% ± 3.4
1930-1938	302	91	61	67.0% ± 4.9
1938-1939	98	39	29	74.4% ± 6.9
1939-1940	103	39	30	77.0% ± 6.7

The prognosis of acute opium poisoning is however very serious as soon as coma sets in. During the period July, 1930 to July, 1940, 503 cases of opium poisoning were accepted for treatment in our emergency clinic (Table 2). In 169 patients coma developed. Of these, 120 (71% ± 3.47) died. In 1939 and 1940 the incidence of opium poisoning increased considerably. Table 2 shows that during these 2 years the mortality of the coma cases was somewhat but not significantly increased. Of the 302 cases of opium poisoning observed between 1930 and 1938, 91 went into coma, 61 of whom died (67% ± 4.9). Of the 98 cases of opium poisoning observed in 1938 to 1939, 39 cases went into coma, 29 of whom died (74.4% ± 6.95). In 1939 to 1940, again 39 cases with coma due to opium poisoning were observed, 30 of whom died (77% ± 6.74).

Until April, 1941, the following routine for the treatment of opium

poisoning was followed: 1, Evacuation of the stomach by gastric lavage with several liters of dilute potassium permanganate ($\frac{1}{5000}$). 2, Administration of an antidote, usually charcoal, a laxative (magnesium sulfate) and high colonic irrigation. 3, Stimulation of the heart action by hourly caffeine injections. 4, Every patient with a depression of the respiration below 8 per minute was placed in a Drinker apparatus.

The emptying of the stomach by gastric lavage presents an important problem because in these patients the gastric lavage often leads not only to aspiration pneumonia but also to fatal damage of the circulation. The general rule that comatose patients should not be lavaged cannot be followed in opium poisoning. In this condition pyloric spasm usually sets in and considerable amounts of the ingested opium are still in the stomach long after the coma has started. Under these circumstances gastric lavage is vitally necessary even in comatose patients. On the other hand the danger of aspiration pneumonia is in hardly any other condition greater than in opium poisoning, and at the autopsy of patients with opium poisoning extensive bronchopneumonia is nearly always found. Many of the patients who in 1938 and 1939 survived had to go through a stormy period of bronchopneumonia or lung abscess, or both.

There are two other factors which complicate the gastric lavage. It has already been mentioned that sometimes patients are still conscious when admitted to the emergency ward, but become deeply comatose during the gastric lavage. This curious experience is not too rare and may perhaps be explained in the following way.

At the time when these patients with opium poisoning are still conscious, the function of their respiratory center is already depressed. The hypernea which follows the introduction of the stomach tube and the gastric lavage with several liters of KMnO_4 solution causes a certain amount of acapnia, sufficient to induce cessation of respiration in these patients with a damaged respiratory center.

In opium poisoning the emphasis has been so much laid upon the respiratory disturbance that not enough attention has been given to the cardiovascular disturbance which is always present in this condition. The considerable increase of the venous pressure which has been observed in experimental animals with morphine poisoning (Gremels³) is a constant feature in our patients with coma due to opium intoxication. The gastric lavage, which is usually accompanied by gagging and struggling, must be highly deleterious to the damaged heart of these patients and may well precipitate the onset of pulmonary edema.

This dilemma—the necessity of emptying the stomach and the possibility of damaging the patient either by inducing coma or pneumonia or heart failure—has caused us much worry. In 1939, we had such a continuous series of bronchopneumonia that we de-

cided to empty the stomach in such cases exclusively by way of a nasal tube. The stomach is lavaged with multiple small amounts of potassium permanganate solution and the solution is allowed to drain out gradually before new permanganate solution is introduced. This method requires a longer time than lavage by means of a ordinary stomach tube; but we have the impression that by this technique the chances for an aspiration pneumonia and for cardiac damage have been reduced considerably. The administration of potassium permanganate solution is continued until the solution returns unchanged. As long as opium is present in the stomach, the fluid drained from the nasal tube turns yellow due to the reducing properties of the opium.

Until April, 1941, when new methods of treatment were introduced we had to use the Drinker apparatus in the majority of the comatose cases of opium poisoning. We have had days when our two Drinker apparatus were both in use at the same time for patients with opium poisoning, so that when a third case arrived we had to take out the patient whose respiration was the least depressed in order to accommodate the newcomer.

It is remarkable that the artificial respiration in a Drinker apparatus evidently does not influence the mortality of opium poisoning. It is possible that the patients with complete cessation of respiration can be kept alive for some time but ultimately death cannot be warded off. In 1934, our first "mechanical lung" was installed, but the statistics from 1930 to 1934 and from 1934 to 1940 do not show any difference in mortality, whether all the cases of opium poisoning or only the coma cases are considered (Table 3).

TABLE 3.—NO INFLUENCE OF USE OF DRINKER APPARATUS (INTRODUCED END 1934) ON MORTALITY IN COMA DUE TO OPIUM POISONING.

Years.	Total cases.	Coma cases.	Deaths.
1930-1934	106	30	19
			63.3% \pm 8.8
1934-1938	196	61	42
			69.0% \pm 5.9
1938-1940	201	78	59
			75.6% \pm 4.9

Therefore, notwithstanding all these efforts the mortality of the patients with opium poisoning after coma had set in, was and remained at the depressingly high level of 70% to 80%. Lately we have tried other methods.

An effective treatment of acute opium poisoning has to cover three main points: 1, to counteract depression of the respiratory center; 2, to prevent pneumonia; 3, to heed cardiovascular damage due to opium.

We have different drugs at our disposal which reputedly have a specific stimulating effect upon the respiratory center. One of these drugs, lobelin, which works favorably in opium poisoning of the

experimental animal, we have tried repeatedly but without success. Of the newer respiratory stimulants three have to be mentioned, namely, coramine, cardiazol or metrazol, and picrotoxin.

Picrotoxin has an excellent effect in barbiturate and avertin intoxication but in experimental opium poisoning, coramine and metrazol are more potent stimulants of the respiration. Of these two drugs coramine seems to be the more advisable. Both drugs must be given in considerable amounts in order to obtain effect in opium poisoning, and in these quantities both drugs may give rise to convulsions. Although in opium poisoning this convulsive action is largely reduced, still it seems preferable for clinical purposes to use coramine which gives a wider margin between the curative and the convulsive dose than metrazol.

Coramine, a pyridine derivate—the diethylamide of pyridine carbonic acid—was introduced around 1924 as a stimulant for the heart action. The opinions about the merits of coramine as a cardiac stimulant are still divided.^{4,5,6,7} For our purpose the action of coramine on the respiratory center is important. Already in the first publication about this drug Uhlmann⁸ emphasized that the depression of the respiration caused by morphine poisoning in the rabbit can easily be neutralized by coramine. After the administration of coramine the deeply narcotized animal wakes up and seems completely normal. The action of coramine, however, is of shorter duration than that of morphine and therefore it is usually necessary to repeat the injection of coramine. In view of these experimental results Uhlmann advised trying coramine in morphine poisoning. The experiments of Maloney and Tatum⁹ published in 1931 and of Gremels³ agree with Uhlmann's results.

Probably due to the rarity of opium and morphine poisoning in the West only a few casuistic reports have appeared in the literature about favorable results of coramine treatment in opium poisoning (Lethaus,¹⁰ Gotsch¹¹). In the literature the emphasis is put upon the curative action of coramine in avertin accidents (Killian,¹² Kennedy¹³), and in barbiturate poisoning (Schula,¹⁴ Das¹⁵). For barbiturates picrotoxin and cardiazol seem to be more effective than coramine (Burstein and Rovenstine,¹ Maloney¹⁶).

In view of the experimental results of Uhlmann, Gremels, Maloney and Tatum, and of the scattered favorable reports in the clinical literature, we have tried since April, 1941, to treat patients with coma due to opium poisoning with intravenous, sometimes intramuscular injections of large quantities of coramine.* The intravenous administration of one or more injections of 5 cc. of the commercial solution of coramine (25%) to a patient who is comatose due to opium poisoning, is often followed by a remarkable improvement. A patient whose respiration is depressed to one or two superficial sighs per minute, who is deeply comatose and cyanotic, some-

* Put at our disposal by the Ciba Company, Summit, N. Y.

times wakes up immediately after the first injection. However, if the case is serious this treatment has to be repeated several times at intervals of a few minutes.

Slight convulsive action may result but usually only a certain amount of rigidity is observed. Most of the patients treated with large doses of coramine experience severe itching of the skin and the eyes. It happens that after a few hours drowsiness sets in again, but a new injection which now can be given intramuscularly is usually sufficient to wake the patient up.

In opium poisoning constriction of the pupils is one of the most constant signs. When this constriction gives way to dilatation, evidently the very last stage of the poisoning has set in. By then, not only the respiratory center but other centers must have become affected and coramine is no longer of avail. The same holds true for the majority of the patients who present symptoms and signs of lung edema.

Left-sided heart failure evidenced by tachycardia and lung edema occurs especially in patients who as is often the case in Peking have already been "treated" before they are admitted. In some cases reviving drugs, sometimes also potassium permanganate solution, have been forced down the throat of the comatose patient. In another instance the coma was first thought to be due to CO poisoning and the patient had been exposed to cold for 2 hours before she was brought to the hospital. However, the patients who were really lavaged outside the hospital, but without the precautions mentioned above, were often admitted with lung edema. Such patients are usually only temporarily revived by the coramine treatment. They wake up, may even talk, the respiration improves, but many of them die after 4 to 5 hours notwithstanding our therapeutic trials under progressive tachycardia and continuous lung edema. In these cases the damage to the circulation has evidently been so serious that no repair is possible. Only exceptionally venesection and intravenous administration of digitalis and ouabain, combined with the coramine treatment, have been able to ward off the fatal outcome.

In order to save also the severest cases of coma due to opium poisoning the coramine treatment must be supplemented with other measures and precautions.

We have found it desirable to try also to prevent the development of bronchopneumonia. A good many of our patients show on admission extensive wheezing sounds. Other patients remain drowsy for several hours even after the coma has subsided. Therefore we have added to our routine the intravenous injection of 1 gm. of sodium sulfapyridine* dissolved in 20 cc. of water every 4 hours until the patient can swallow the sulfapyridine. This sulfapyridine treat-

* Put at our disposal by Lederle Laboratories, Inc., New York.

ment is continued for at least 24 hours after the subsidence of the coma.

Gastric lavage by means of a nasal tube, magnesium sulfate and charcoal are also given in order to remove and to neutralize as much as possible of the opium introduced.

When the pulse is rapid digitalis or ouabain have been injected intravenously. Intravenous infusions of considerable quantities of saline with or without glucose have not been given in order to avoid overfilling of the circulation with ensuing overstrain of the left ventricle. This might have been deleterious in patients with opium poisoning whose circulation is already damaged and many of whom are on the verge of pulmonary edema. Subcutaneous infusions of 500 cc. NaCl 0.9% have been given repeatedly.

Only rarely have the injections of coramine given rise to convulsions. In these cases 2 gm. of chloral hydrate have been administered by rectum. The same drug was given to patients who after being revived from the coma were excited or even delirious.

The following two examples may illustrate the result of the coramine treatment. In the first case the reaction was prompt and the danger had disappeared shortly after the treatment was started. In the second patient 7 injections of 5 cc. coramine each, in the course of 2½ hours, were necessary before consciousness returned.

CASE 1.—A Chinese housewife, 37 years old, was brought to the emergency clinic on October 3 at 11.30 p.m. in a comatose state. She had taken 2 dollars worth of opium 4 hours previously and was found to be unconscious ½ hour before arrival at the clinic.

On admission she was totally unconscious. Lips and finger nail beds were cyanotic. Respiration was shallow and at the rate of 12 per minute. Pupils were constricted. Corneal reflex was absent. Pulse was good, 96 per minute. Heart sounds were distinct and cardiac rhythm was regular. Blood pressure was 170/100 mm. Hg.

After brief examination the patient was given 5 cc. coramine intravenously, together with 20 cc. 5% sodium sulfapyridine solution. Immediately following the injection the patient became conscious, opened her eyes, moved about and cried bitterly. The cyanosis at once disappeared and her respiration became deep. There was no spasticity of the limbs.

Gastric lavage with a nasal tube was done after the patient became conscious. The gastric washing became clear after 4500 cc. 1 to 5000 potassium permanganate solution had been used. Following the lavage, 50 cc. 20% charcoal suspension and 50 cc. 50% magnesium sulfate solution were given through the nasal tube.

The patient was given 2 more injections of coramine, in 5 cc. doses, intramuscularly during the next 2 hours. Sodium sulfapyridine in 1 gm. doses was given intramuscularly every 4 hours. The patient was encouraged to take strong tea after she became conscious. She was sent home in good condition 17 hours after the commencement of treatment. Three days later she was seen again and found to be in excellent condition. The gastric washing was found to contain morphine.

CASE 2.—A Chinese rickshaw puller, 35 years old, was brought to the emergency clinic on October 15 at 2:50 p.m. in an unconscious state. He had taken 5 dollars worth of opium. He was found to be unconscious at 1.30 p.m.

On admission the patient was comatose. The skin and nail beds were very cyanotic. He had Cheyne-Stokes respiration and the respiratory rate was 6 per minute. The pupils were constricted and did not react to light. The corneal reflex was absent. The pulse was good, 96 per minute. The cardiac rhythm was regular and the heart sounds were distinct. Blood pressure was 100/60 mm. Hg. Knee jerks were absent.

Treatment was started at 2.55 P.M., when 5 cc. coramine were given intravenously. Patient remained unconscious and cyanotic. Only the corneal reflex became active. At 3.02 P.M. 5 cc. coramine and 20 cc. 5% sodium sulfapyridine were given intravenously. No change was observed. At 3.12 P.M. 5 cc. coramine were given intramuscularly. There was no change in his condition. He was cyanotic and unconscious. His corneal reflex was absent again. There was no spasticity of the limbs. At 3.20 P.M. 5 cc. coramine were given intravenously. Two minutes after this injection the patient woke up and was able to say a few words. His respiration improved and the cyanosis lessened. He was, however, soon seized with marked generalized spasticity of the body and he became excited and struggled a great deal. In order to reduce the restlessness and excitement 2 gm. chloral hydrate in solution were given per rectum. He became quiet gradually; the spasticity of the muscles also greatly lessened.

At 4.15 P.M. patient had become totally unconscious again, with absence of corneal reflex and marked cyanosis. His respiration was 8 per minute. His pulse was good. Coramine, 5 cc., was given intravenously at 4.30 P.M. Except for slight improvement in his respiration there was no change in his condition following this injection. The corneal reflex remained absent and the cyanosis was not lessened.

At 5.20 P.M. 5 cc. coramine were given intravenously. Following this injection the patient immediately woke up and talked. The cyanosis disappeared and his respiration became deep. There was much spasticity of muscles, although no convulsion occurred; 5 cc. coramine were given intramuscularly shortly after the intravenous injection. The patient was somewhat delirious for about $\frac{1}{2}$ hour, but he became gradually mentally clear. No more coramine was given.

Gastric lavage with nasal tube was performed from 3 to 7 P.M. Only after 10 liters of permanganate solution had been used did the return fluid no longer change color. Charcoal suspension and magnesium sulfate were given through the nasal tube following the lavage.

Sodium sulfapyridine, 1 gm. every 4 hours, was given intramuscularly following the first intravenous dose. The patient had no fever during the period of observation.

The patient was discharged in good condition 2 days after the commencement of treatment. He was seen again 3 days later and was found to be in good condition. The gastric washing was found to be positive for morphine.

We have been able to apply this treatment between April 1 and November 1, 1941, to 46 cases of opium poisoning where coma had already set in. Twelve of these patients died and 34 recovered (Table 4). The total mortality is therefore $26.1\% \pm 6.5$, which is significantly different from the mortality of the years 1939 ($74.4\% \pm 6.95$) and 1940 ($77\% \pm 6.74$). Patients admitted with dilated pupils always died with or without treatment with coramine (Table 5). We have therefore analyzed separately the influence of the coramine treatment on the coma patients with non-dilated pupils and also on the coma patients with cyanosis and with non-dilated pupils

(Table 4). The results are always markedly and significantly better after the coramine treatment has been introduced.

TABLE 4.—MORTALITY RATE IN ACUTE OPIUM POISONING WITH COMA BEFORE AND AFTER INTRODUCTION OF THE CORAMINE TREATMENT.

Signs: Year.	Coma cases.		Coma with non-dilated pupils.		Coma with cyanosis and non-dilated pupils.	
	Total.	Mortality.	Cases.	Mortality.	Cases.	Mortality.
1938-1939 . . .	39	29 74.4% \pm 6.9	32	22 68.8% \pm 8.2	24	20 83.4% \pm 7.6
1939-1940 . . .	39	30 77.0% \pm 6.7	38	29 76.4% \pm 6.9	28	22 78.6% \pm 7.8
Apr.-Nov., 1941 . . .	46	12 26.1% \pm 6.5	42	8 19.0% \pm 6.0	34	7 20.6% \pm 7.0

TABLE 5.—MORTALITY RATE IN ACUTE OPIUM POISONING WITH COMA AND DILATED PUPILS.

Signs: Year.	Coma. Total.	Coma with dilated pupils.	
		Cases.	Mortality.
1938-1939	39	7	7
1939-1940	39	1	1
Apr.-Nov., 1941	46	4	4

Of the 12 patients we lost during the coramine period 4 had dilated pupils and 5 showed marked lung edema at admission. Therefore, the life-saving effect of coramine is on the whole limited to patients with opium poisoning as long as the pupils are constricted and no pulmonary edema has set in. Then, however, it is usually possible to save the life of the patient, even if the respiration has already practically stopped, if Cheyne-Stokes breathing is present, if the patient is deeply cyanosed or ashy colored, and if the cornea reflexes have disappeared. It is possible that the results would have been still better if a good many of the patients with opium poisoning who came for treatment had not been damaged by previous lavage outside the hospital.

The amounts of coramine which were deemed necessary to revive the patients have greatly varied as shown by Table 6.

TABLE 6.—AMOUNT OF CORAMINE USED.

Dosage, cc.	Cases.	Deaths.	Dosage, cc.	Cases.	Death.
5.0	5	0	20.0	12	3
6.7	1	0	23.4	1	0
8.4	1	0	25.0	1	1
10.0	7	0	30.0	3	3
14.2	1	0	35.0	3	2
15.0	6	2	45.0	1	1
16.8	2	0	60.0	1	0
18.0	1	0			
			Total	46	12

Although the statistical differences are significant, we still thought it advisable to go into the question whether the coma cases observed during the period of coramine treatment were by any chance lighter than those treated during the 2-year period without coramine. If we take the duration of coma before arrival and the degree of retar-

dation of the respiration as the criteria for the gravity of the intoxication, we see that:

A. Five of the 18 coma patients who survived in 1939 and 1940 were not comatose at the time of admission, a few even walked into the hospital (Table 7). They became drowsy and comatose only shortly after arrival in the emergency ward, especially after or during gastric lavage. Cases of this kind do not belong to the most severe form of opium poisoning. In such patients only a small amount of opium has been absorbed at the time of admission and by gastric lavage the rest can be removed. On the other hand when coma has lasted for several hours before admission the outlook is serious. As only 1 of the 18 survivors had had coma for more than 2 hours before admission, most of the patients of the surviving group of 1939 and 1940 evidently did not have severe cases of poisoning.

TABLE 7.—DURATION OF COMA BEFORE ARRIVAL.

	Duration of coma.	
	1939-1940.	Apr.-Nov., 1941.
Developed after arrival	5	4
Less than 1 hour before arrival	2	3
1 to 2 hours before arrival	6	11
3 to 4 hours before arrival	1	8
5 hours or more before arrival	0	3
Unknown	4	5
Total	18	34

In the coma patients treated with coramine the duration of the coma before arrival was on the whole longer. Of the 34 patients who survived with coramine, 11 patients had been comatose for more than 3 hours before arrival.

B. Of the 18 survivors in 1939 and 1940 before the coramine treatment, only 1 showed Cheyne-Stokes breathing and in no case had the respiration completely stopped. In the period of coramine treatment 10 of the 34 survivors showed Cheyne-Stokes breathing and in 4 patients the respiration had even completely stopped (Table 8).

TABLE 8.—DEGREE OF RETARDATION OF RESPIRATION.

	Respiration.	
	1939-1940.	Apr.-Nov., 1941.
Over 16 per minute	6	5
Below 16 per minute	11	15
Cheyne-Stokes type	1	10
No respiration	0	4
Total	18	34

Therefore, if any difference exists the patients who survived during the coramine period were on the average in a more serious condition than the patients who survived without coramine.

It is well possible, although it cannot be proved, that the combination of coramine plus sulfapyridine has been more effective than the application of coramine alone would have been. We have no statistical data which might prove or disprove this point. It remains, however, possible and even probable that several patients revived by the intravenous injections of coramine would have developed pneumonia if no sulfapyridine had been given.

Summary. Between 1930 and 1940 the mortality of coma due to acute opium poisoning has fluctuated in our hospital between 70% and 80%. The treatment consisted of gastric lavage, charcoal, magnesium sulfate and caffeine injections. As soon as the respiratory rate was decreased below 8 per minute the patients were put into a Drinker apparatus.

Gastric lavage with the ordinary stomach tube often induces coma in patients with opium poisoning. It is also a frequent cause for the development of lung edema. In all serious cases of opium poisoning, certainly when coma has set in, gastric lavage should be performed through a nasal tube in order to avoid excessive gagging and struggling of the patients.

Intravenous injections of 5 cc. coramine, usually to be repeated several times, are able to revive the respiratory center in opium poisoning and to restore consciousness.

The coramine treatment, combined with intravenous injections of sodium sulfapyridine, has reduced the mortality in coma due to opium poisoning from 70%—80% to about 26%.

Even with this treatment the outcome of coma due to opium poisoning is usually still fatal as soon as the pupils are dilated or lung edema has set in.

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A MICRO METHOD FOR DETERMINING PROTHROMBIN TIME ON FRESH CAPILLARY BLOOD USING STANDARD PHYSICAL CONDITIONS.

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THE estimation of the prothrombin content of blood using amounts which may be obtained readily by skin puncture has the advantage of less annoyance to the patient; but, if the same degree of duplicability is to be obtained as is possible by the method of Quick, the same control of physical conditions is required. Unless this accuracy is assured, the advantage scarcely justifies a change of procedure. An attempt, therefore, was made to estimate prothrombin on 0.05 ml. of capillary blood using standardized physical conditions. Since the determination is made immediately after withdrawal, disturbance of calcium from its native state by anticoagulants is unnecessary. Other than this, the method is of practical significance only and has the same theoretical basis as that of Quick.²⁵

Thus, as the essential mechanism for the coagulation of blood, the method uses the Morawitz-Wohlisch equation which requires at least four substances: calcium, fibrinogen, thromboplastin and prothrombin. Since it is a time reaction, the concentration of one of these, prothrombin, may be measured by coagulation time only if the other three are present in such concentrations that they are not limiting factors. Except in rare instances,^{21,26} calcium and fibrinogen in their native state fulfill this requirement.^{5,6,25,10a} Practically, it is easily possible to alter this concentration if necessary.²⁴ Thromboplastin of optimal potency has probably not yet been obtained and many reports have appeared indicating that the standard and near optimal potency described by Quick was not used. When thromboplastin becomes a limiting factor, absolute values are no longer comparable and relative ones (*i. e.*, per cent of normal) have not been shown to be strictly so.

Prothrombin estimations have been made by many variations of the methods of Quick,²⁵ of Smith *et al.*²⁹ and of Dam.⁷ A brief résumé is presented in Table 1. Conversion time of prothrombin to thrombin dissociated from the reaction time of thrombin on fibrinogen have not yet been assigned their places in the clinical laboratory. Therefore, the simplicity and ready duplicability of the

method of Quick has resulted in wider adoption of it than of the two-stage technique of Smith, Warner and Brinkhous.²⁹ The use of Stypfen as a substitute for thromboplastin in the Quick procedure is of singular interest.¹⁰ The values reported by Fullerton for normal plasmas equal his values for thromboplastin but do not equal those of Quick. Such values were obtained by Felicity, Hobson and Witts⁸ when lecithin was added to Stypfen.

As shown in the résumé, several investigators have used so-called micro amounts of whole blood for the determination. Quick used them in an approximate method.^{25c} Although the endpoint is more easily read with plasma, the substitution of whole blood in his original method made no difference in the results.^{25c} Kato adapted the plasma method of Quick to micro proportions using oxalated whole blood.¹⁷ Others (see Table 1) have omitted anticoagulants and modified the method of reading the endpoint.

In our experience skin puncture does not permit a sufficiently free flow of blood to obtain 0.2 ml. smoothly. As a result, closely duplicable values were not routinely obtained. The results are referable to those of Quick only on the percentage basis. Therefore, we attempted to estimate prothrombin on 0.05 ml. fresh, whole blood at 37.5° C. using thromboplastin which had a potency of at least 12.5 seconds by the method of Quick.

Technique. Only one reagent is required to carry out the procedure, thromboplastin extract, prepared according to Quick,^{25b} and having a potency of at least 12.5 seconds on normal plasma. These preparations have been rather constant in potency. Those of rabbit lung have been more potent and at least as constant as those of rabbit brain. When they are acceptable they assay, on standard normal plasma, 10 to 11.5 seconds. If they are not of this potency they are markedly lower. Of a series of 25 rabbits, studied when no rabbit brain obtained from animals locally available gave acceptable preparations, 19 assayed less than 12.5 seconds, 1 as high as 8.5 seconds. If the lung showed signs of congestion or appeared filled with blood, values up to 14.5 seconds were obtained. The brains of these same animals yielded extracts which assayed 12 to 12.5 seconds in 5 instances; less than 14 in 15 instances. Since this time (over a year) only an occasional preparation has been unacceptable. In the aforementioned series, admittedly inadequate in number, no relation to age, size, breed or diet was observable. Quick has mentioned that season may have an effect. These preparations of low potency were made in a very warm season but fully potent extracts *i. e.*, 10 to 12.5 seconds, were made the following year under equally adverse weather conditions. Greater care has perhaps been used to keep the preparations cold immediately after their processing and during their immediate desiccation on the Florsdorf-Mudd Cryochem apparatus. Fractions sealed *in vacuo* and kept in the dark at 3° C. have kept their potency for at least 17 months (*i. e.*, when the last fraction was used).

Most of the apparatus required are routine hematologic equipment: a glass micro culture slide with two depressions 18 mm. in diameter and 1.75 mm. deep, two pipettes graduated at 0.05 ml.,* a sharp lancet (prefer-

* A convenient pipette is made by Ace Glass Company, distributed also by Scientific Equipment Company, 3527 Lancaster Ave., Philadelphia. In addition to the calibration mark it has a tapered tip which is slightly constricted.

TABLE 1.—SUMMARY OF OTHER METHODS FOR DETERMINING PROTHROMBIN TIME.

Author.	Substrate.	Type of thromboplastin.	Essential procedure (vol. in ml.).	Temperature control, ° C.	Method of reading endpoint.	Range of normal (sec. or %).	Remarks.
A. ONE-STAGE TECHNIQUES.							
Agee et al. ¹ 1938	Oxal. plasma from 4.5 ml. blood	Saline extr. of acetone residue of rabbit brain (Quick)	0.1 plasma, 0.1 plaslin + 0.1 CaCl ₂ . "Optimal" dilutions of CaCl ₂ and of plaslin	37	Tilt tube	22-25 sec.	According to Quick standard curve.
Allen et al. ² 1940	Oxal. plasma from 4.5 ml. blood	Saline extr. of dried perfused dog lung (Warner et al.)	0.1 plasma, 0.1 plaslin + 0.1 M/40 CaCl ₂ , using serial dilutions of plasma below 50%	37	Tilt tube	e. g. 27.6 sec. at 50%.	Confirmatory.
Bergami et al. ³ 1940	Oxal. plasma from 4.5 ml. blood	Saline extr. of rabbit brain	As in (1) but "optimal" temperature and serial dilutions also used	39	Tilt tube	15 sec.	Approximate. Excess calcium.
Carpenter ⁴ 1941	App. 0.1 ml. blood	1 drop blood, 1 drop plaslin, lyophilized powder, + 1 drop M/40 CaCl ₂	Air current on surface (aided by lyophilized powder).	Held constant at 3 min. Interp. in terms of percent of plaslin req. for nor. by R (index) K (unknown) /K (normal).
Dam et al. ⁵ 1938	Heparinized plasma from 3.8 ml. blood	Ringer extr. of gray matter macerate of human brain	0.1 plasma + 0.1 plaslin varying the concentration so that the coag. time is 3 min.	39	Mechanical device tilts tubes every 15 sec.	Checks Quick values within 2 sec.
Folcety et al. ⁶ 1941	Heparinized plasma from 3.8 ml. blood	Stypfen* 1:10,000 to 1:10,000 + 0.5% lecithin	0.1 plasma, 0.1 lecithin-stypfen + 0.1 M/40 CaCl ₂	(Optimal: 37-43) 38.5 ?	Tilt tube	11 sec. (20 with venom alone)	Expressed as % normal using con.: time as direct proportion.
Fischer et al. ⁷ 1940	Oxal. blood, 0.15 ml.	"Quick" ?	0.15 blood, 0.15 plaslin + 0.15 M/40 CaCl ₂	38	Tilt slide and prick with platinum wire	14-16 sec.	Expressed as % normal using con.: time as direct proportion.
Fullerton ⁸ 1940	Oxal. plasma from 4.5 ml. blood	Stypfen* 1:10,000	0.2 plasma, 0.2 plaslin + 0.2 M/40 CaCl ₂	37.5	Tilt tube	18-25 sec.	Expressed as % normal using con.: time as direct proportion.
Holmboe et al. ⁹ 1940	Oxal. plasma from 4.5 ml. blood	Saline extr. of acetone ppt. from ether extr. of acetone residue	0.2 plasma, 0.2 plaslin + 0.2 CaCl ₂ . Vary all 3 for "optimal"	37 until actual test	Tilt tube and rotate in air every 15 sec.	60-80 sec., av. 70 100%	Expressed as % normal using con.: time as direct proportion.
Huber et al. ¹⁰ 1940	Fresh cap. blood, 0.2 ml. "	Saline extr. of ground beef or pig lung	0.2 plaslin + 0.2 blood	Room. Simultaneous control	Prick every sec. with stylus	100%	

Innes et al. ¹⁶ 1941	Oxal. blood app. 0.1 ml.	Stypven* 1:10,000	0.1 blood (oxal. 1 + 9 in w.b.c. pipette), 0.1 Stypven + 0.1 M/40 CaCl ₂	Room. Simultaneous control	Visual, against white background	25-35 sec. prothrombin index	Index normal time/test time × 100. See Smith (Ziffren ²³).
Karabin et al. ¹⁶ 1940	Fresh cap. blood, 0.3-0.4 ml.	Saline extr. of ox brain (lung) diluted to normal coag. time of 20-30 sec.	0.3-0.4 blood + 0.1 plastin	Room. Simultaneous control	Tilt slide	100%	Expressed as % normal using con.: time as direct proportion.
Kaump et al. ¹⁸ 1940	Oxal. plasma from 4.5 ml. blood	Saline extr. of acetone residue of rabbit brain	0.2 plasma, 0.1 plastin + 0.1 M/40 CaCl ₂	Room, 21-25	Tilt tube	19-24 sec.	
Kato ¹⁷ 1940	Oxal blood, 0.2 ml.	Acetone residue from macerated rabbit brain, saline extract	0.1 blood, 0.1 plastin + 0.1 M/40 CaCl ₂	Room	Tilt slide. "Fixation of clot"	20 ± 2 sec.	
Lawson ¹⁹ 1941	Fresh cap. blood, 0.2 ml.	Quick thromboplastin dried overnight at 37° C.	0.2 ml. blood + 0.2 ml. thromboplastin. Mix with glass rod	Room up to 80° F.	Tilt slide	19-20 sec.; over 75 is abnormal	
Mazatl ²⁰ 1939	Oxal. plasma	Saline extr. of air dried brain	See Quick	37.5 special device	Tilt slide	18-22 sec.	
Palmer ²² 1941	Oxal. blood, 0.15 ml.	Commercial tissue extract—Astra.	Blood in Ellerman tube. 0.15 blood, 0.15 plastin + 0.15 CaCl ₂ , M/40	38	Test with Pt or steel loop	15-25 sec.	
Plum et al. ²¹ 1940	Heparinized blood, 0.1-0.2 ml.	See Dam. ⁷ Diluted so that normal is 25-35 sec.	Blood, 0.1, heparinized in pipette, discharged into 1 drop plastin. 0.2 blood when prothrombin = 10%	Room	Tilt tube	25-35 sec. but result is prothrombin index	See Dam. ⁷
Pohle et al. ²¹ 1939	Oxal. plasma from 4.5 ml. blood	Saline suspension of rabbit brain. Inactivate at 50° C. 15 min.	0.1 plasma, 0.1 plastin + 0.1 CaCl ₂ . CaCl ₂ concentrations varied to "optimal"	37.5	Tilt tube	10 sec. (less also). (Gross lipemia, e. g., 8.5)	
Quick ²² 1935-40 1939	Oxal. plasma from 4.5 ml. blood Fresh cap. blood, app. 0.05 ml.	1940: saline extr. of acetone residue of rabbit brain or lung 1940: saline extr. of acetone residue of rabbit brain or lung	0.1 plasma, 0.1 plastin + 0.1 M/40 CaCl ₂ 0.05 ml. plastin + 0.05 ml. blood	37.5 "Over lamp"	Tilt tube Tilt slide	12.5 sec. (less also, more potent plastin)	Type method.
Russel et al. ²¹ 1941	0.2 ml. cap. blood, oxalated	1:10,000 Russel viper venom	0.2 ml. blood + 0.2 ml. venom + 0.2 ml. CaCl ₂ , M/40	Room	Tilt slide	28 sec. or less	
Sherber ²³ 1940	Citrated plasma from 5.5 ml. blood	Saline extr. of ground fetal (human) brain	0.1 plastin, 0.1 M/40 CaCl ₂ at 40° C. for 30-45 min. + 0.1 plasma	40 special device	Visual, black background	10-13.3 sec., av. 12.1 ± 0.7	

* Russel viper venom.

TABLE 1—Continued.

Author.	Substrate.	Type of thromboplastin.	Essential procedure (vol. in ml.).	Temperature control, °C.	Method of reading endpoint.	Range of normal (sec. or %).	Remarks.
Senter et al. ²⁰ 1910	Oxal. plasma from 4.5 ml. blood	Lyophilized saline extr. of air dried rabbit brain	See Quick's ²⁵	37.8	After 15 sec. tilt tube in air	21?	Calcium added to unoxalated blood.
White et al. ²² 1911	Fresh cap. blood, 0.1 ml.	Acc. to Quick's original method	0.1 blood, 0.1 plasmin + 0.1 M/40 CaCl ₂	Room	Tilt slide. Check with glass rod	Av. 27.7	Use concentration: time as direct proportion. Type method.
Ziffren et al. ²³ 1939	Fresh venous blood, 1 ml.	Saline extr. of ground ox or rabbit brain or lung. Acceptable potency, 25-60 sec.	0.1 plasmin + 0.9 ml. blood	Room. Simultaneous control	Tilt tube	100% of normal	
Herbert ¹¹ 1940	Oxal. plasma	CaCl ₂ -saline extr. of acetone residue of rabbit brain	B. TWO-STAGE 0.1 plasma (diluted 1:25; 1:50; 1:100; 1:200), 0.1 glyoxaline buffer, 0.2 CaCl ₂ plasmin, 0.2 mixture + 0.1 fibrinogen	TECHNIQUES. 37-38	Suction with capillary pipette	Expressed as % of normal	Finds thrombin con. direct proportion to time. Considers Quick values conversion time (Ob. Quick values, 22-40 sec.).
Jaques ¹⁵ 1911	As in Smith ¹²	As in Smith ¹²	Defibrinate with thrombin. Dil. serially to 100 times. 0.3 dil. plasma + 0.1 imidazole buffer + 0.3 thromboplastin + 0.1 1% CaCl ₂ + NaCl (0.85%) to 1.2 ml. Compare with standard thrombin	20° C.	Tilt tube	210 units	Depends on dilution to free of antithrombin. Standard thrombin acc. Mellanby.
Smith et al. ²⁴ 1935-1910	Oxal. plasma from 13 ml. blood	Saline extr. of ground beef lung. Adjust to pH 7.1 before use. 1935: saline extr. of dried perfused dog lung	0.1 plasma, defibrinated with thrombin and diluted (1:20; 1:30; 1:40; etc.), 0.1 saline, 0.1 plasmin, 2% CaCl ₂ . Mixture (containing 2% acacia), incubated for various periods + 0.1 fibrinogen. "Optimal" plasmin concentrations used	28	Tilt tube	Held to 15 sec. 284 units (i. e., 84% of dog. Av. dev., 8.8%)	Values read from standard curve. Registers complete conversion of all (if none undenatured) prothrombin.
Thordarson ²¹ 1940	Oxal. plasma	Saline extr. of ground beef lung. Filter. Inactivate at 60° C.	Plasma diluted serially, range 4-1%. 0.3 fibrinogen, 0.3 plasmin, 0.3 CaCl ₂ , 0.3 di-ethyl-barbiturate. Incubate to constant activity. Add 0.3 plasma	37	Mechanical device. Tilt tubes every 15 sec.	Interpreted in terms of similar Thunberg method for citric acid	Antithrombin effect contr. by dil. Activation time greater for greater dil. Prothrombin concentr. and time not directly proportional.

regarded as significant the difference between values for undiluted plasma and for plasma diluted to 12.5%

ably of the rebound type), sterile gauze sponges, a stopwatch (split-second type), a rake with platinum prongs* (three 12 mm. lengths of 24 B-D gauge platinum wire sealed into a 9 cm. length of glass rod), an alcohol lamp (gas burner), and a slide warming device. For this, it is possible to use a hot-water bottle, protected from drafts; the outside temperature being brought to 37.5° C. Far better is the slide incubator which has been especially designed for the test† (Fig. 1). It consists of a small compartment (approx.

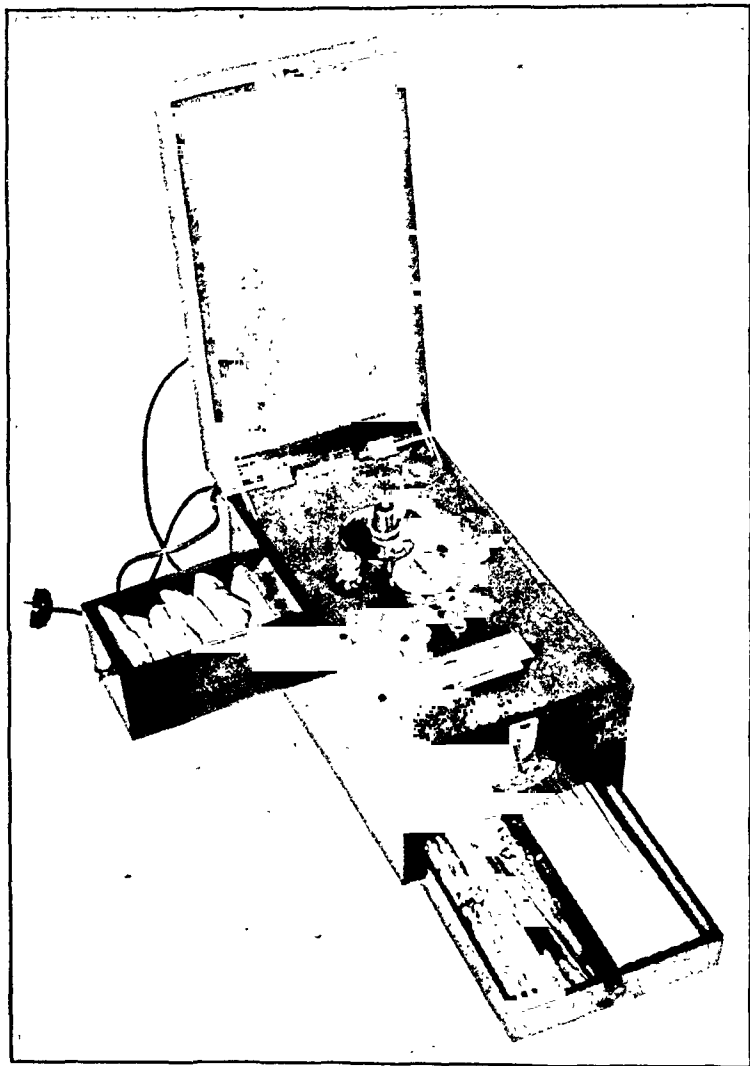


FIG. 1.—Apparatus for performing test with slide indicator.

6 by 5 by 3 inches), well insulated on three sides while the top, closed partially by insulation, has a window the dimensions of a slide. This window is closed by a sheet of copper which serves as a support for the slide and as a heat distributor. The heating element consists of a 7 watt sub-stage lamp inserted into the compartment. Between the lamp and the heat

* Suggested by the platinum hook used in the method for determining coagulation time devised by Dr. Pearl Lee, unpublished.

† May be obtained from the LaMotte Chemical Products Company, Towson, Baltimore, Md.

distributor, a sensitive bimetallic thermoregulator is mounted. A thermometer is placed beside the slide on the copper sheet. This unit has been built into a box which contains other compartments for the rest of the equipment needed to carry out three tests. This is a convenience when the test is to be made at the bedside.

The procedure for making a prothrombin estimation follows: The slide is placed in the apparatus and brought to 37.5° C. The finger is cleaned with undenatured 70% alcohol. The thromboplastin extract (0.05 ml.) is placed in each of the two depressions in the slide. The finger, or the side of the heel if the patient is an infant, is pricked to obtain a free flow of blood. This is obtained more easily if the area of puncture is warm. After discarding the first 2 drops of blood, 0.05 ml. is taken up into a pipette. This is immediately discharged into the thromboplastin on the slide. The stopwatch is started, the mixture is stirred with a rake (previously cleaned

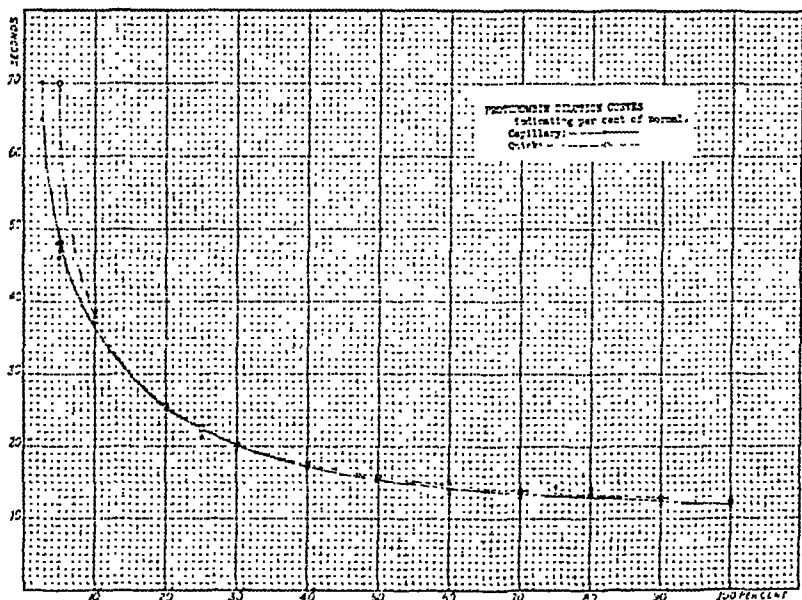


FIG.—2.—Standard dilution curve.

by flaming and carbon free) and stroked once each second after 10 (or 12, depending upon the potency of the extract). The instant the clot as a whole moves is taken as the endpoint. A duplicate is then made from a fresh prick, starting the endpoint strokes $\frac{1}{2}$ second later.

This prothrombin time may be converted to terms relative to the normal by reading them on the dilution curve in Figure 2 when the thromboplastin extracts assay 12 seconds for normal plasma. For extracts of other potencies it is necessary to prepare standard dilution curves for the respective preparations. Those assaying between 10 and 13 seconds may be corrected mathematically to give usable values.

Experimental Considerations. To test the reliability of the method it was compared with that of Quick in three ways. First, dilution curves were prepared using standard thromboplastin and plasmas shown to be normal and constant in amount, one for well over a year. The dilutions were made with saline in a few instances but the fibrin

web was too fragile in the lower concentrations for accurate reading of the endpoint. Dilutions were then made with saline solutions of fibrinogen prepared from oxalated, citrated and from heparinized plasmas. However, in the lower dilutions, where larger amounts of fibrinogen were required, indications of anticoagulant impurities made themselves evident although the preparations were dialyzed. Therefore, fibrinogen was prepared* from hemophilic blood (a suggestion of Dr. Ferdinand Monroe) which had a coagulation time of 4 hours. Saline solutions of this material were used in obtaining the data for the curve shown in Figure 2. If the effect of plasma proteins on added calcium is disregarded, the calcium concentration was kept constant by drying in the slide depressions aliquots of an $M/40$ CaCl_2 solution necessary to maintain 10 mg. per 100 cc. calcium. The calcium redissolves in the thromboplastin extract when it is placed on the slide. In obtaining the data for the curves, the appropriate aliquots of blood were taken up directly into a 0.1 ml. pipette, followed by fibrinogen-saline to the 0.05 ml. mark, mixed by tilting the pipette to and fro and discharged into the calcium-thromboplastin mixture. The rest of the technique was that of the routine procedure.

A second comparison was made on a series of clinical cases. One series was studied by the same investigator using the same reagents, the bloods being taken almost simultaneously. In another, the two procedures were carried out by independent investigators using their own apparatus and reagents. (We are indebted to Dr. John Reinhold, Chief Biochemist of the Philadelphia General Hospital for the Quick values.) In this group several hours elapsed between the collection of the samples for the Quick method and those for the capillary procedure. In the latter a hot-water bottle served as a temperature unit. A third comparison was made on the assay values of the two methods on thromboplastin extracts of various potencies. These were obtained almost simultaneously.

Discussion. As shown in Figure 2, the micro capillary procedure gives a curve which may be very nearly superimposed upon that of Quick. The slope tends to be a little steeper at the higher concentrations and tapers off more gradually below 10%. The only foreign chemical introduced into the preparation of the former was $(\text{NH}_4)_2\text{SO}_4$ (no anticoagulant was used). Whether the scarcely significant differences between the Quick values and those of the micro capillary method are due to these factors or to technical artifacts cannot be stated. The effects of other plasma proteins was not studied but Quick does not report a divergence in his dilution curves made with saline from those with deprothrombinized plasma.

* The fibrinogen was prepared by half saturation with $(\text{NH}_4)_2\text{SO}_4$. It was reprecipitated 4 times from normal saline and dialysed 18 to 24 hours at 3° C. Its saline solution, which was concentrated 6 times from the original plasma was prothrombin-free in the presence of 10 mg. per 100 cc. calcium.

TABLE 2.—PROTHROMBIN TIMES IN CLINICAL CASES.

(A Comparison of the Values by the Quick Method with those by the Micro Capillary Procedure.)

Diagnosis.	Quick (seconds).	Micro capillary (seconds).
<i>A. Same Reagents and Technician (Simultaneously).</i>		
Normal	11.0	11.5
	12.5	12.5
	12.5	12.5
Chronic calculous cholecystitis	12.5	12.5
	12.5	12.7
	13.0	12.8
Carcinoma of lung	13.5	14.3
Rectosigmoid carcinoma	13.7	13.5
	14.0	13.7
Melena	14.0	13.0
Acute cholecystitis	14.2	14.6
Hemophilia	14.7	14.2
Bile peritonitis	14.7	15.0
Tuberculous enteritis	15.3	15.8
Subdiaphragmatic abscess	15.5	16.5
Polycythemia vera	21.0	20.5

B. Independent Reagents and Technician (Same Day).

New-born hypoprothrombinemia (after vitamin K)	12.5	13.0
Chronic calculous cholecystitis	12.5	13.0
Pneumonic bacteremia XI	13.0	12.5
Diabetes mellitus	13.0	13.0
Acute catarrhal jaundice	13.0	13.0
Pneumonic bacteremia XI	13.0	15.0
Chronic calculous cholecystitis	13.0	16.0
Carcinoma, primary; cholelithiasis	14.0	14.0
Sydenham's chorea	14.5	15.0
Carcinoma (primary?); cholelithiasis	15.0	15.0
	15.0	16.0
Adenocarcinoma of duodenum	22.0	21.0
Chronic myelogenous leukemia with jaundice	42.0	189.0

(in extremis)

TABLE 3.—STANDARDIZATION OF THROMBOPLASTIN EXTRACTS.
Simultaneously by:

Quick's method (seconds).	Capillary method (seconds).
12.5	13.5
12.5	12.5
13.0	12.0
14.0	14.5
16.0 *	19.0
16.5	17.0
17.0	16.0

In assays of the thromboplastin extracts (Table 3) and in the series of clinical cases (Table 2), the values for the two methods check usually within 5% of prothrombin, always within 10%. Since the Quick procedure uses plasma and the capillary method whole blood, the values in polycythemia are interesting. For the case in Table 2, the volume of packed cells was 79%, the volume index 1.08 and the erythrocyte count 7,200,000. Nevertheless the two methods checked. However, after lysing the cells into their plasma with distilled water and restoring the calcium concentration

to 10 mg. %, the prothrombin value decreased. over that for normal blood similarly treated, in proportion to the hematocrit. Since the cells, in untreated blood, do not actively dilute, the concentration of prothrombin in blood and plasma remains the same. This is true also for bloods for which the hematocrit values are abnormal. In the micro capillary procedure the increased concentration of cells may, by their added viscosity, aid in reading the endpoint, *i. e.*, in moving the clot as a whole. The absolute amount of both fibrinogen and of prothrombin are less in these samples. As in enzyme systems, the conversion of prothrombin to thrombin plus the action of thrombin on fibrinogen, as measured by the one-stage techniques, seems to be a function of concentration not of absolute amounts.

It would appear from these data that the micro capillary procedure here described can serve as a substitute for the Quick procedure where venipuncture is undesirable and where it is required to obtain the value at the bedside. It approaches the Quick method for accuracy and is by its use of native calcium more physiologic but requires somewhat greater skill to read the endpoint. Whatever error results from tissue juice contamination in samples taken without pressure from a finger prick is inherent in the method.

Summary. A practical micro method for the estimation of prothrombin on fresh capillary blood has been suggested. By dilution curves and by simultaneously estimating the prothrombin content of normal and pathologic bloods, the micro capillary method shows a parallelism with the Quick values usually within 5% prothrombin, certainly within 10%. Since physical conditions are controlled as in the original Quick procedure, values are comparable both in absolute and in relative terms. A variation in hematocrit caused no divergence.

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DIAGNOSTIC CRITERIA AND RESISTANCE TO THERAPY IN THE SPRUE SYNDROME.

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THE sprue syndrome (celiac disease—sprue) is, as a rule, amenable to proper therapy, although, from the great variations in its symptoms, one would not expect constant uniformity in therapeutic results. Celiac disease, which is the childhood analogue of adult sprue, has been shown¹ to respond very satisfactorily to parenteral liver extract when the vitamin B complex is added. Celiac disease bears the same relation to sprue that cretinism does to myxedema.

In adult sprue, whether occurring in warm or cold climates

("tropical" and "non-tropical" sprue being identical), the response to parenteral liver extract, with a diet low in fats and rich in proteins and vitamins, is, in the great majority of patients, prompt and dramatic. Such patients quickly regain their lost appetites, eat ravenously and often gain 1 pound a day; the tongue returns to normal and the diarrhea ceases promptly. Concomitantly a sense of happiness and well-being replaces the former feeling of depression and despondency.

Such is the usual result, but now and then a patient is encountered who, though fulfilling the most stringent diagnostic requirements of the sprue syndrome, yet responds poorly or not at all to adequate liver and dietary therapy. This communication aims to direct attention to 4 such cases which have occurred among 60 instances of the sprue syndrome studied during the past 7 years in the Duke Hospital Clinic.

The diagnostic requirements of the syndrome, to which we have adhered with the utmost rigidity, are these:

1. *Steatorrhea*. In 48 cases of this series the average amount of fat in the dried stools was 48.5%. In normal individuals the stool fat does not exceed 15% of the dried weight, and on the usual diet is even lower. *Sprue cannot be diagnosed in the absence of steatorrhea*, demonstrated quantitatively, though steatorrhea does occur, of course, in other diseases.

2. *Loss of Weight*. This is practically a constant finding and may equal or exceed that seen in any other condition. Losses of from 25 to 70 pounds are the rule and not infrequently the patient has lost as much as he weighs on admission. One patient, a woman of 51, had lost 98 pounds in 1 year.

3. *Low Glucose Tolerance Curve*. The sprue patient exhibits very constantly a rise of less than 40 mg. per 100 cc. in the blood sugar curve when given 1 gm. of glucose per kilo of body weight. As a rule, the rise is very slight and no rise at all may occur. The average rise in blood sugar in 54 of our cases was 20 mg. per 100 cc. If the patient has received liver the rise may exceed 40 mg. per 100 cc., since under the influence of liver therapy the blood sugar tolerance curve rises rather rapidly. Despite the fact that such low glucose tolerance curves are found in some 5% of normal people, as well as in disease states other than the sprue syndrome, the constancy of its occurrence in sprue gives it great value in completing the clinical picture.

4. *Anemia*. In our experience the fully developed sprue syndrome in adults practically always exhibits a macrocytic-hyperchromic anemia, which cannot be distinguished either by peripheral blood or bone marrow studies from the hematologic picture of pernicious anemia. The bone marrow of children seldom reacts in a macrocytic-hyperchromic manner to any injury, and it is thus not surprising that a reaction of this type is very rare in celiac disease.

5. *Hypochlorhydria and Achlorhydria.* Low acid values in gastric contents after histamine stimulation are commonly seen in untreated sprue, the acid values rising, however, with fair rapidity after successful liver and dietary treatment. Histamine-refractory achlorhydria does not occur in sprue more often than in normal individuals. In 56 cases, normal values were found in 22%, hypochlorhydria in 57% and achlorhydria after histamine in 21%. *It is thus seen that 79% of patients suffering from the sprue syndrome could be differentiated on admission from pernicious anemia by gastric analysis alone.*

There are other features of the sprue syndrome, such as a sore, reddened and depilated tongue, with or without aphthous ulcers; a pendulous, gaseous abdomen, with a much distended colon, and certain Roentgen ray findings common to several other deficiency states, which fill in the clinical picture, but the five findings described above are highly characteristic of the sprue syndrome, and unless present one should be very reluctant to make this diagnosis. It should be emphasized, however, that the sprue syndrome is in nowise hazy and ill-defined; if the disease is studied with all modern resources its differential diagnosis is clear and precise. Without such studies it is impossible to make the diagnosis in many instances, and no report in the literature upon the sprue syndrome can be regarded as fully reliable unless the data essential to a correct diagnosis, as detailed above, have been assembled. For this reason much of the literature is more confusing than informative.

It is not infrequently impossible to establish the diagnosis of sprue without a *quantitative estimation of the fats in the stool*. The following method for the determination of total stool fats was developed in this clinic by Dr. Raymond Reiser, and has been found sufficiently accurate for clinical use.

Method. Reagents: 9N sulfuric acid (approximately); 95% ethyl alcohol; ethyl ether, U.S.P.; petroleum ether, U.S.P.

Make stool sample to viscous consistency with distilled water, mixing well to homogenize. If large particles still remain, strain through a No. 8 strainer.

1. On an analytical balance weigh to milligrams a 5 to 10 gm. sample in a tared 50 cc. pyrex beaker. Dry in oven at approximately 115° C. for about 3 hours. This will yield dry weight of stool, and can be carried on during the fat extraction, which is carried out on another sample as follows:

2. At the same time weigh out to milligrams a 3 to 5 gm. sample of the watery homogenized stool directly into the bottom of a 50 cc. round-bottom, narrow-neck centrifuge tube, taking care to keep material from sides of tube. Add 1 cc. of 9N sulfuric acid and make to approximately 5 cc. with water. Add to this an equal volume of 95% ethyl alcohol. Heat in boiling water bath for 2 minutes. Cool thoroughly under running water. Add 15 cc. of ethyl ether, stopper with cork stopper, and shake vigorously. Add 15 cc. of petroleum ether, stopper, and shake vigorously. Centrifuge at low speed for 3 minutes. Transfer the clear supernatant fluid to a shallow-bottom, 50 cc., conical centrifuge tube. Evaporate the ether cautiously by heating the tube in a small beaker of hot water, taking precautions to prevent bumping. For this purpose a small special stirring rod, with a

curved, beaded tip, is placed in the tube. Repeat the extraction of the alcoholic stool mixture 4 or 5 times using 15 cc. portions of ethyl ether and petroleum ether each time as before, and evaporating the supernatant cautiously after each extraction.

The residue from the extractions remaining in the conical centrifuge tube is dried by heating the tube in boiling water bath for 10 minutes, making sure that no alcohol, ether, or water remains in the tube. Cool and add 30 cc. of petroleum ether, washing down stirring rod and sides of tube, and stirring up residue well. Centrifuge at low speed. Transfer the clear supernatant fluid to a tared 50 cc. Erlenmeyer flask. Evaporate the petroleum ether slowly by heating cautiously on a steam bath. Repeat this extraction with 30 cc. portions of petroleum ether 4 times, transferring the supernatant to the 50 cc. Erlenmeyer flask and evaporating off the petroleum ether each time. After the last evaporation no petroleum ether should remain.

Dry the flask on the outside and place this flask and the beaker from "1," containing the oven-dried sample of stool, in a vacuum desiccator for 1 hour. Weigh the beaker to milligrams and the flask to tenths of milligrams, using an analytical balance.

Calculation:

$$\frac{(\text{gm. of stool before drying}) \times (\text{gm. of fat in flask}) \times (100)}{(\text{gm. of dried stool}) \times (\text{gm. of stool taken for fat extraction})} = \% \text{ fat in dried stool.}$$

The following differential possibilities must be considered in the diagnosis of the sprue syndrome: 1, pernicious anemia; 2, multiple avitaminoses; 3, pancreatic disease; 4, tabes mesenterica; 5, gastrocolic fistula; 6, anorexia nervosa; 7, Simmonds' disease. These need not be considered in detail in this place. Pernicious anemia presents the greatest difficulties, and it is with this disease that the sprue syndrome is most often confused. One may say briefly and confidently that if the five characteristic features of the sprue syndrome, as enumerated above, are borne in mind the differential diagnosis of the syndrome presents no serious difficulty.

As the following 4 histories are presented to illustrate only one point, namely, that the sprue syndrome in certain instances may prove refractory to treatment, only the essential details will be given.

Case Abstracts. CASE 1 (Duke Hosp., No. A-51386). A married woman, aged 28, since the age of 5 or 6, has had attacks of diarrhea, especially in the summer, lasting a few days, with 6 to 8 stools daily. With these attacks she had abdominal cramps, nausea and vomiting. She has always been "anemic" and underweight.

During her first and only pregnancy she vomited a great deal and became so anemic that she remained in the hospital for a month postpartum under treatment with liver and iron. A few months later she began to have severe diarrhea, with 15 to 25 stools daily, severe prostration, nausea, vomiting and rapid loss of weight. At this time the diagnosis of sprue was made and liver therapy, iron and a "diet low in fat and carbohydrate with bananas" were given. She improved, but had several more attacks of the same kind, until about 3 years ago she was admitted to her local hospital weighing only 69 pounds. After "liver and banana" therapy for 3 weeks she improved and her weight was 105 pounds on discharge.

The course of the ailment during the past 3 years has been steadily

unfavorable, with frequent bouts of nausea, vomiting, diarrhea and alternating gains and losses in weight.

Physical and Accessory Examinations. The patient was very thin, weighing 90 pounds (best weight 115 pounds). The stools were grayish-brown in color, unformed, and the average of 5 determinations of fat in the dried stools was 42%. The *glucose tolerance test* on admission showed a rise of 2 mg. per 100 cc.; a second test done 8 months later, after adequate liver and dietary therapy, exhibited a rise of only 11 mg. per 100 cc. The blood on admission showed: R.B.C. 3,800,000, Hgb. 13.2 gm. (85%), M.C.V. 101, M.C.H.C. 35.4 $\cdot 10^{-12}$, C.I. 1.14, reticulocytes 0.8%, W.B.C. 5800. Eight months later the R.B.C. were 4,200,000, Hgb. 13.8 gm. The *fasting stomach contents* showed total acid 33°, free HCl 25°; after histamine (0.5 mg.) total acid 59°, free HCl 57°.

Comment (Case 1). The history and physical findings are typically those of the sprue syndrome except for the rather indefinite account of attacks of diarrhea from childhood on. These may well have been due to sprue, for the syndrome may begin at any age. The patient received very adequate treatment with liver extract, yeast (Vegex), iron and a diet low in fats but adequate in proteins and vitamins. Her response to treatment has been very poor and she continues to suffer from the symptoms with which she was first seen.

CASE 2 (Duke Hosp., No. 70486). A man, aged 56, for 2 years before admission had noticed progressive weakness and gradual loss of weight, and for the past year has had intermittent bouts of diarrhea, with the passage of 4 to 5 stools, large in volume, light yellow in color and foul smelling. His continued loss of strength brought him to the hospital.

Physical and Accessory Examinations. Except for marked evidences of *loss of weight* and edema of the feet and legs, the physical examination was not important. He had lost some 30 pounds in 2 years. The stools were semiliquid, silver-gray in color, foul-smelling, looked fatty and were greasy to touch. Of the dried 24 hour stool, 37.8% was fat. Oral *glucose tolerance test* showed a rise of 10 mg. per 100 cc. *Blood*: R.B.C. 1,100,000, Hgb. 6.3 gm. (41%), C.I. 1.72, hematocrit 21 vols. %, M.C.V. 144, M.C.H.C. 52, W.B.C. 4900. The *fasting stomach contents* showed total acid of 10°, free HCl 0; after histamine total acid 89°, free HCl 80°.

Course. This patient was admitted to Duke Hospital 3 times from July, 1936, to April, 1939. On the first admission the diagnosis of sprue was registered and adequate treatment given to which he made a satisfactory response, gaining 1,690,000 R.B.C. and 4 gm. of hemoglobin in 26 days. The diarrhea ceased and he felt very well, but gained no weight.

Despite careful instructions as to therapy, and several requests by letter for his return to the clinic, he was not seen until nearly 2 years later. At that time he had lost so much weight as to be merely "skin and bones." He reported that during the preceding year the diarrhea had returned and that he had grown so weak that he had been forced to remain in bed in the County hospital.

On the second admission nothing new was discovered, although all former tests, Roentgen rays and so on were repeated, except signs of sub-clinical tetany, with blood values for calcium of 4.8 mg. per 100 cc., and for phosphorus of 2.5 mg. per 100 cc. A hyperchromic-macrocytic anemia was still present, 35° of free HCl were found after histamine; fat in the stool was 56% of the dried weight. The therapeutic response to liver, iron, calcium and a high vitamin, high caloric diet was very unsatisfactory.

The reticulocyte response to liver extract was only 2.4% with a R.B.C. count of 1,900,000, and he gained in 30 days of treatment only 650,000 R.B.C. and 1.5 gm. of hemoglobin.

One year after his second admission he was sent by the County social welfare service for a third admission. His failure to improve in health had made him dependent upon public support and his condition on admission was that of advanced sprue cachexia. He was now given maximum liver therapy parenterally and orally, together with all dietary aids, but he failed completely to respond to therapy.

The R.B.C. on admission were 2,300,000, Hgb. 9.3 gm. and were almost the same on discharge after 4 weeks of intensive liver therapy, during which he received from 30 to 60 U.S.P. units daily.

Forty-seven per cent of the dried stool was fat; there was a rise of only 13 mg. per 100 cc. in the glucose tolerance curve and there were 91° of free HCl in the stomach contents after histamine stimulation. He died 1 month after discharge. No autopsy.

Comment (Case 2). The 2 instances of the sprue syndrome, just detailed, though not presenting evidences of unusual severity, yet proved almost totally refractory to the most intense liver and dietary therapy. It must be emphasized that we have seen many patients much more ill in appearance than were either of these 2, but who responded rapidly and most satisfactorily to far less liver therapy than these 2 patients received.

CASE 3 (Duke Hosp., No. A-13088). A man, aged 21, was admitted on 3 occasions, twice for diagnostic studies of only a few days' duration, during which no treatment was given, and a final admission of 4 days which terminated by death, with autopsy. The diagnosis "sprue" was registered on each admission and proper treatment advised.

He had been a normally healthy child, with no history of any intestinal trouble. At the age of 14 he began to have bouts of diarrhea at intervals of from 1 to 3 months, passing 4 or 5 watery stools daily. During such attacks his appetite failed and he suffered from mild abdominal "gas pains," relieved by defecation.

It is impossible to say how much treatment he received, but he was given liver intermittently. Gradually the periods of diarrhea became more frequent, of longer duration and were accompanied by anorexia, vomiting and marked weight loss, which was regained in part during the periods of remission. In the 4 months just preceding his final admission he lost 60 pounds (average weight 130; admission weight 70). He has suffered from soreness of the tongue and mouth.

Physical and Accessory Examinations. On his final admission he was terribly emaciated, weighing 70 pounds, and was described as "just skin and bones." *Stools:* these had the appearance of "light yellow, foamy soup," and 56% of the dry weight was fat. A *glucose tolerance test* showed a rise of 14 mg. per 100 cc. The *blood* showed constantly a mild macrocytic-hyperchromic picture, with a M.C.V. ranging from 91 to 98 and a color index of from 1 to 1.3. On the final admission ascorbic acid, carotene and vitamin A were absent from the blood plasma. The *fasting stomach contents* showed no free HCl but, after histamine stimulation, 16° were found.

Comment (Case 3). Owing to the patient's obviously very serious condition he was given maximum treatment with liver extract and all the available vitamins, intravenously. He showed no improvement whatsoever and died after 10 days.

The *autopsy* failed to demonstrate a cause of death. There was great emaciation and loss of fat everywhere, with microsplanchnia. The mucosa of the entire gastro-intestinal tract appeared quite normal. The pancreas and adrenals were normal in appearance. Permission could not be obtained to open the cranium.

CASE 4 (Duke Hosp., No. A-29848). A woman, aged 30, was admitted following a 3 months' stay in another hospital, where she was under the care of an experienced physician who had made the diagnosis of sprue and carried out what seemed to be intensive and adequate liver and dietary treatment, together with iron and anterior pituitary extract. A glucose tolerance test had revealed that there was no rise whatever in the curve (fasting sugar 100 mg. per 100 cc.; at $\frac{1}{2}$ hour intervals it was 83, 83, 86, 90, 100 mg. per 100 cc.). She was transfused on several occasions.

Eight months previous to admission she had developed malaise, weakness, slight anorexia and a diarrhea which had steadily increased in frequency and severity. She passed from 4 to 8 large clay-colored foul-smelling stools daily. In 1 month she lost 13 pounds and on admission weighed 73 pounds. Her condition on admission was obviously serious in the extreme. One observer described her as "one of the most realistic examples of skin and bones that I have ever seen." She had lost some 30 pounds. The tongue was beefy red, dry and quite devoid of papillæ. She swallowed even liquids with difficulty. *Stools*: these were thick-liquid, light colored and contained 51% and 54% fat on 2 occasions. Proctoscopic examination showed no ulcerations or abnormalities, and the stools did not contain blood. Owing to her condition no glucose tolerance test or gastric analysis was done. The report from the hospital from which she was transferred stated that there was no free HCl in the gastric contents after histamine stimulation. There were 3,750,000 R.B.C., Hgb. 13.9 gm., color index 1.2. There was marked anisocytosis with macrocytes predominating; red cells were filled with hemoglobin.

As pointed out above, the patient had received adequate treatment for sprue before admission; but in view of her desperate condition liver extract was administered both intravenously and intramuscularly in maximum doses, together with glucose and several blood transfusions. She was given adequate amounts of nicotinic acid, riboflavin and thiamin chloride and calcium gluconate intravenously, but in spite of this heroic therapy she became progressively weaker and expired on the tenth day.

The *autopsy* findings in this patient were almost exactly similar to those of Case 3. With the exception of moderate edema of the entire gut, nothing abnormal was found. The pancreas was small but so were all the abdominal viscera. No structural cause of death could be established.

Summary and Conclusions. The essential criteria for the diagnosis of the sprue syndrome (celiac disease—sprue) are detailed.

The physical character of the stools in sprue is an unreliable diagnostic aid, since this varies from "dirty dish-water" to the classic large, foamy stools of the text-books. A quantitative estimation of fat in the stools is the only reliable evidence of steatorrhea.

Abbreviated histories of 4 sprue patients are given, all of whom exhibited marked refractivity to the form of treatment which in the great majority of patients suffering from the sprue syndrome yields prompt and brilliant results. In other words, under certain conditions the morbid process appears to be irreversible. The reason for this occasional refractivity is not known.

Three of the 4 patients died, and 2 were examined postmortem. The autopsy findings were similar in every way to those reported by other observers, being those of extreme inanition only, and inadequate to explain the fatal outcome.

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THE APPARENT CURE OF PERIARTERITIS NODOSA WITH SULFAPYRIDINE.

REPORT OF A CASE.

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PERIARTERITIS nodosa is no longer thought to be a hopeless malady. During recent years, several cases of this disease have been reported which were characterized by marked chronicity, remissions and apparent cures.

The purpose of this paper is to report a case of periarteritis nodosa in a negro male which was successfully treated with sulfapyridine. The response to the therapy was prompt and the patient is apparently well 19 months after the cessation of treatment.

No attempt was made to make a complete survey of the literature. Only those cases showing spontaneous remissions or therapeutic responses were analyzed.

Carling and Hick¹ reported the gradual recovery from an active phase of periarteritis nodosa with the use of intravenous injections of arsenicals. Several months later the patient was apparently well except for some evidence of generalized muscular wasting.

Schottstaedt⁶ treated a 41-year-old barber with neosalvarsan. The patient gradually improved and after several months was apparently cured. Approximately 2 years later the patient was still in a state of "remission."

Macaigne and Nicaud³ reported the occurrence of periarteritis nodosa in a female who suffered her initial attack at the age of 27 years. After a latent period of 5 years, she had crises of increas-

ing severity every year for about 10 years. The treatment consisted of general systemic and symptomatic measures. The patient was alive at the time the paper was published.

Martin *et al.*⁴ described a case which had existed for 10 years and was characterized by five separate crises. In the first crisis, "I.O.D." vaccine and injections of milk relieved her symptoms. Incision of "fixation abscesses" resulted in a favorable response in the second, third, and fourth crises. Arsphenamine may have benefited the fifth crisis but recovery was not evident at the time the report was published.

Motley⁵ treated a 31-year-old male with general physiologic measures, blood transfusions, small doses of neoarsphenamine, and a high vitamin diet. The patient gradually improved and was well several months later except for residual neurologic changes. His subsequent course was not known.

Vining⁷ reported a case of a 7-year-old female whose illness lasted 22 months, during which there were five phases of active illness. No specific therapy was used. She was well at the time of the published report 1 year after discharge.

Lindberg, according to Vining,⁷ reported a case of a child 15 years of age who was treated with iodides and recovered after an illness of 4½ years' duration.

Grant² reports 7 cases, 4 of which were still alive. The essential treatment in these was one of supportive measures.

Case Report. The patient, J. W., a negro male, aged 22, entered the hospital on April 14, 1940, complaining of aching pains in the legs, neck, and general weakness of 8 days' duration.

He stated that the onset of his present illness began with dull aching pains in the legs, right arm and neck. The pain was so severe that he was unable to stand or use his arm. Aspirin gave only temporary relief. At no time did he notice any swelling of the joints. The pain became localized in both calf muscles and the right biceps. Chills and fever were associated with these pains. Shortly after the onset, a small nodule appeared in the left forearm which he described as about the size of a "buck-shot."

He had the usual childhood diseases. A tonsillectomy was performed 15 years ago. He was not subject to attacks of pharyngitis or tonsillitis. He gave no history of attacks similar to his present illness.

The family and marital history were essentially negative.

He worked in a C.C.C. camp 6 months prior to the onset of the present illness. His eating and sleeping habits were of a normal character.

Physical Examination. The patient was a well-developed and well-nourished negro male who was lying in bed under a heat tent and appeared to be in acute distress, especially whenever he attempted to move his right arm or legs.

The temperature was 100° F., pulse 80, respiration 22, blood pressure 100/58 mm. Hg. He weighed 125 pounds. The examination of the heart and lungs revealed normal findings. There were no enlarged organs or masses in the abdomen, and no tenderness was elicited on deep palpation. The muscles of the neck were tender but there was no limitation of motion. The muscles of the arms and forearms, particularly the flexors, were tender with a 90% limitation of motion. Small, firm, freely movable, moderately tender subcutaneous nodules measuring 0.2 to 0.5 cm. in diameter were

present on the volar surface of each forearm in the region of the ulna. There was no evidence of muscular atrophy. The calf muscles of both legs were extremely tender, but there was no limitation of motion and no nodules. All reflexes were physiologic. Examination of the fundi disclosed no abnormalities.

Laboratory Examination. An EPA view of the chest revealed no evidence of pulmonary disease. The heart and great vessels were of normal size and configuration. An electrocardiogram revealed no evidence of myocardial disease.



FIG. 1.—Photomicrograph of nodule from left forearm ($\times 112$). Area showing three small arteries in cross-sections with surrounding fibrosis and inflammatory cell infiltration. Vessel walls infiltrated with inflammatory cells. Each vessel is thrombosed.

Hematologic studies revealed 4,600,000 red blood cells per c.mm. Hemoglobin 95% (Sahli), white blood corpuscles 21,500 per c.mm., neutrophils 77%, lymphocytes 11%, monocytes 11%, basophils 1%. The sedimentation rate was 20 minutes (Linzenmeier method). Urinalysis revealed no abnormal findings. The blood chemistry was as follows: urea nitrogen 14 mg. per 100 cc., glucose 80 mg. per 100 cc., icterus index 16.5, cholesterol 150 mg. per 100 cc. Phenolsulphonephthalein and Fishberg kidney function tests were within normal limits. Kline and Kolmer tests of the blood were negative. Blood agglutinins for typhus, typhoid, paratyphoid and undulant fever were all negative and remained so on subsequent examinations.

The biopsy of the forearm revealed an elliptical shaped piece of skin measuring about 1.5 cm. in length and 0.8 cm. in diameter with about 0.8 cm. of subcutaneous tissue attached to the central portion. Serial paraffin sections, stained with hematoxylin and eosin, were made of the entire specimen. One inflammatory focus (Fig. 1) in the subcutaneous tissue consisted of three small arteries cut in cross-section which were envel-

oped in edematous connective tissue heavily infiltrated with lymphocytes, macrophages and neutrophils. A similar type of tissue was present in the area between each vessel. The wall of each artery was markedly thickened because of inter- and intracellular edema of the muscular coat and a heavy infiltration with inflammatory cells which were predominantly neutrophils. Eosinophils and lymphocytes made up the remainder of the cellular exudate. Each of the three vessels was thrombosed and showed extensive necrosis of the endothelium. In some of the sections where the endothelium was still preserved, marked hydropic degeneration of the endothelial cells was present. In two of the vessels no internal elastic lamina was identified but in the third, small, swollen portions still remained. Other vessels throughout the remainder of the tissue showed less extensive changes. Most of these vessels were very small arterioles which showed hydropic degeneration of the muscular coat and of the endothelium, accompanied by a perivascular infiltration of lymphocytes. Perivascular fibrosis was present about most of the vessels.

Course in the Hospital. The patient was given a high caloric, high vitamin diet. Salicylates, barbiturates, and opiates were administered to relieve pain. Heat was applied to the body surfaces by means of a heat tent. All of these procedures gave only temporary relief. A nodule from the left forearm was taken for biopsy 4 days after admission (Fig. 1). During the first 2 weeks in the hospital the patient developed sudden severe, cramp-like abdominal pains simulating those seen in mesenteric arterial occlusion. His temperature fluctuated between 99.5° F. and 101° F. during the first 2 weeks in the hospital. During the early part of the third week the temperature gradually rose and fluctuated between 100.8° F. and 103° F. At the end of the third week he had lost 35 pounds in weight. On the twenty-second hospital day he was given an initial dose of 45 gr. (3 gm.) of sulfanilamide followed by 80 gr. (6 gm.) daily for 6 days. There was no therapeutic response to the drug.

The patient was then given 15 gr. (1 gm.) of sulfanilic acid and 7½ gr. (0.5 gm.) of sodium bicarbonate 3 times daily for 14 days, but failed to respond to this therapy. The blood leukocytes remained elevated but the red blood cells fell to 2,900,000 per c.mm.

Sulfapyridine was started on the thirty-ninth hospital day at which time the temperature was 101.5° F. An initial dose of 4 gm. was given, followed by 1 gm. every 4 hours. The dosage was reduced to 0.5 gm. every 4 hours when the blood sulfapyridine reached a high level. Within 12 hours the temperature dropped to 99° F. and remained between 99° and 100° F. for the next 12 days. Sulfapyridine was then discontinued for 2 days during which time his temperature rose to 101.7° F. Following resumption of the drug the temperature gradually fell and reached normal 8 days later, when the drug was discontinued. No further elevations in temperature occurred. A total of 156 gm. of sulfapyridine was administered over a period of 32 days. The blood sulfapyridine levels ranged between 6 mg. per 100 cc. and 18.6 mg. per 100 cc., with the average level being 10.8 mg. per 100 cc. Just prior to his discharge from the hospital the red blood cells had increased to 3,600,000 per c.mm., and the hemoglobin to 60% (Sahli). The white cell count was normal. The sedimentation rate was normal. Repeated electrocardiograms revealed no evidence of myocardial disease. He had regained 18 of the 35 pounds he had lost in the early part of his illness. The nodules were no longer palpable and the patient was without complaints. He was discharged on July 31, 1940, 106 days after admission to the hospital, the last 3 weeks of which he was completely free of symptoms.

He was readmitted 6 weeks later for a checkup examination. A routine physical and laboratory examination was made and all tests found to be within normal limits. He had gained 12 additional pounds.

Since his original discharge 19 months ago, we have seen him on three occasions, the last being on February 11, 1942. During this time he has been doing manual labor and enjoying perfect health.

CASE 2. H. R., colored female, aged 6 years, with history of repeated attacks of pain in knees, wrists, and elbows, associated with fever and painful nodules in skin for past $1\frac{1}{2}$ years. During her stay in the hospital, the temperature was between 99° and 103.2° except for an occasional period of 1 or 2 days.

A diagnosis of periarteritis nodosa was made by biopsy of a subcutaneous nodule.

She was given sulfapyridine for 1 month during which time the average blood level was 9.2 mg. per 100 cc. The temperature remained relatively low, 99° to 100° , while sulfapyridine was administered. Because of the low grade fever, the possibility of a drug reaction presented itself and sulfapyridine was discontinued. The temperature returned to normal 19 days later where it has remained for 5 weeks. Associated with the return of normal temperature, there was a disappearance of all nodules, marked clearing of the edema of upper eyelids, return of normal sedimentation rate, and a feeling of well-being.

Comment. Case 1 is the first case of periarteritis nodosa which was diagnosed antemortem at the Charity Hospital in New Orleans.

The diagnosis was definitely established by biopsy 1 week following his admission to the hospital, and 2 weeks after the onset of his illness.

The prompt response to sulfapyridine therapy after other therapeutic measures apparently failed, would seem to indicate that the drug had some specific action. Support of this view is evidenced by the elevation of temperature following the withdrawal of the drug as well as the drop in the temperature when the therapy was resumed.

It is reasonable to assume that the early diagnosis which permitted the early institution of sulfapyridine therapy, accounted for the good response in this case.

The infiltration of eosinophils into the acute arterial lesions is probably due to the local response to degenerating muscle in the vessel wall. There was no peripheral eosinophilia or any other evidence of an allergic state.

Summary. 1. A case of periarteritis nodosa which was successfully treated with sulfapyridine is reported.

2. The patient is apparently well 19 months after treatment.

3. The institution of treatment relatively early in the disease was probably an important factor in the favorable result obtained.

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BOOK REVIEWS AND NOTICES

THE PRINCIPLES OF NEUROLOGICAL SURGERY. By LOYAL DAVIS, M.S., M.D., PH.D., D.Sc. (HON.). Pp. 503; 298 illustrations and 5 colored plates. Second Edition. Philadelphia: Lea & Febiger, 1942. Price, \$7.00.

To have compressed the principles of neurologic surgery into less than 500 pages and to have included in these pages the gist of all that a neurosurgeon needs to know about his specialty is no mean feat in terse and compact writing. Other authors have covered various special subjects of course in greater detail, but this is the only textbook known to the Reviewer in which all the problems thrown into the neurosurgeon's lap from spina bifida to hypertension and from cranio-cerebral injuries to the surgery of pain are briefly and intelligently discussed. The first chapter comprises a review of the anatomy and physiology of the nervous system; brief to be sure, but entirely adequate. The second chapter on cranio-cerebral injuries is not as satisfactory a discussion of an important subject as are those that follow. Nothing is said of the treatment of compound fractures or of penetrating wounds of the skull. The discussion on intracranial tumors, diagnosis, classification, pathologic types, results of treatment, is excellent, giving the student or general practitioner all that he needs to know on these subjects. Brain abscess, bone infections and cysts and tumors of the skull are adequately considered. The surgery of the cranial nerves begins with a short but excellent account of the symptoms, diagnosis and treatment of major trigeminal neuralgia. Finally lesions of the last four cranial nerves are described. Spinal cord injuries and their treatment and the diagnosis, localization and management of the various types of spinal cord tumors comprise the next two chapters. Turning from the spinal roots to their endings in the peripheral nerves, an excellent description is given of the diagnosis and treatment of injuries to these structures. This is one of the most satisfactory chapters in the book. From the peripheral nerves the logical step is a description of how to relieve the most distressing symptoms of irritation or compression of these structures, namely, pain. The indications for rhizotomy, cordotomy or section of the cervico-thoracic or lumbar sympathetic chains are clearly described in these very enlightening chapters. The next sections include a consideration of the value of surgery in the treatment of epilepsy, a short summary of the diagnosis and proper management of cervical rib, syringomyelia and traumatic arterio-venous aneurysm, hydrocephalus and spina bifida. The last 50 pages are given over to a discussion of the surgical treatment of hypertension. An excellent short review is included of the experimental investigations upon which this treatment is based.

As may be gathered from this brief review, this book touches upon all branches of neurosurgery. The author states in his preface that he makes no pretense at including an exhaustive treatise upon each subject considered, but hopes to give to the practitioner of medicine and to the medical student easily assimilable facts which will aid them in obtaining a more accurate concept of neurologic surgery to the end that their patients will receive accurate and sound advice.

This purpose, the Reviewer feels, has been adequately accomplished. The author has for the most part sifted his facts with sound judgment and omitted much that is non-essential. His publishers have provided him with a clear, legible type and the privilege of using many excellent illustrations.

F. G.

MEDICAL DISEASES IN TROPICAL AND SUB-TROPICAL AREAS. Reprinted by permission of the Controller of His Britannic Majesty's Stationery Office. First American Edition. Pp. 282; 108 figures. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1942. Price, \$4.75.

To quote from the preface, "This, the sixth edition of the Memoranda—is in no way to be regarded as a substitute for any of the excellent treatises on Tropical Medicine available, nor does it claim to cover the whole range of tropical medicine; rather it is intended as a handy manual for use in the field. . . ."

The "List of Contents" will best indicate the subjects covered—Beriberi, Cerebro-spinal Fever, Cholera, Diarrhœa, Dysentery (Bacillary), Heat-stroke, Jaundice, Paratyphoid Fever, Plague, Relapsing Fever, including Tick Fever, Scurvy, Small-pox, Sprue, Trench Fever, Typhoid Fever, Typhus Fever, Undulant Fever, Yellow Fever.

Each of the diseases that has been included is discussed briefly but adequately; etiology, symptoms, prognosis, diagnosis, differential diagnosis, prophylaxis and treatment being given. Representing, as it does, the work of many authorities and being an official publication of the British War Office, the book needs no further recommendation. It should be in the hands of every medical officer of the Army of the United States and should not be neglected by physicians in civil life. H. R.

FEDERATION PROCEEDINGS, a Quarterly publication by the Federation of American Societies for Experimental Biology. Editorial Board, W. O. Fenn, Chairman; Philip Bard; C. G. King; Morton McCutcheon; C. F. Schmidt; and A. H. Smith; D. R. Hooker, Managing Editor—19 W. Chase St., Baltimore, Md., 1942. Price, \$4 (\$4.75 foreign).

The first issue of this new publication in March, 1942, contained the complete Federation program of its 5 component Societies. It has been arranged that the June and September issues will contain the full text of 20 or more papers presented at the annual meeting, and the December issue will contain material pertinent to the Federation membership. The publication takes the place of the former "Federation Yearbook" which will be discontinued, as will the publication of abstracts of the component societies in their specialized journals. The new publication should prove of value to libraries, laboratories and individuals wishing to keep abreast of biologic research in North America. It will be distributed to the 1800 Federation members on payment of their society dues. E. K.

ADMINISTRATIVE MEDICINE. HAVEN EMERSON, A.M., M.D., Editor. Pp. 826; several figures. New York and Edinburgh: Thomas Nelson & Sons: copyright 1937, 1940, 1941.

This volume, containing 53 short, concise chapters written by men and women preëminent in their respective fields, is best described by quoting the Editor:

"With the growth of specialization in medical training, skills, and experience, and in part as a sequel of the elaboration and great expense of apparatus for diagnosis and treatment of disease, and still more because of inclusion of the application of preventive and curative medicine among the functions of civil government, there has been an increasing diversion of professional personnel and of collective financial resources from the individuals to the organized use of medical arts and sciences over the past fifty years and more.

"It may be said that almost every member of an American community, whether urban or rural, comes into personal relation with one or many of the voluntary or governmental agencies of medical service each year whether he seeks personal care in sickness or receives in a direct or remote way some protection from the local or state department of health.

"It is primarily to bring to physicians a more precise description of the functions and organization of these institutions and agencies that persons of experience and authority in the various special fields of administrative medicine have collaborated as authors for this volume.

"In Part I is presented the development of organized care of the sick in its chronological sequence from its original, and still its most important, function of general hospital care of bed patients, through to the elaborate and socially precious symbol of public interest in securing the best services of the medical sciences for all who need them.

"In Part II, the arrangement and approach are more according to the patterns of governmental and social structure than along the lines of historical development. First, the official and then the voluntary or non-official health services are dealt with, the international, national, state or provincial, and local city, county, or district."

The volume may help "to correct a common tendency among physicians to concern themselves only with the medical and health needs of their private patients."

R. B.

SEROLOGY IN SYPHILIS CONTROL. PRINCIPLES OF SENSITIVITY AND SPECIFICITY. By REUBEN L. KAHN, M.D., D.Sc. Pp. 206; 31 tables, 1 chart. Baltimore, The Williams & Wilkins Company, 1942. Price, \$3.00.

THE Reviewer has read Dr. Kahn's book as a physician who needs a text in which he "would find, not which serologic test is better or poorer than the other, but considerations of the principles of serology; considerations which would enable them to best utilize these tests in the diagnosis and treatment of syphilis and in the control of this disease." While there are many features of the book which commend it to physicians interested in serology, unfortunately some of the important questions puzzling physicians are left unanswered and much of the good information requires a fairly intense knowledge of the basis of serology for its comprehension.

A recent analysis of 2000 questions that the doctor asks about syphilis (Stokes, Ingraham and Stannard, *Ven. Dis. Inform.*, 21, 147, 1940) showed the blood serologic reaction to be the third problem in interest and that the doctor's inquiries concern: 1, Fixed or irreversible positive serologic tests. No ready reference to a discussion of this important phenomenon could be found beyond the possible use of the quantitative procedure in determining true seroresistance (p. 140). 2, General interpretative questions. This point is covered in a general way insofar as the thesis of the study is to show how far one may depend on serologic reactions in syphilis with regard to sensitivity and specificity; but there is no statement for the practitioner on the meaning of the different reactions reported by the laboratory. 3, Questions of laboratory procedure, relative merits of various tests, shortcuts, and so forth. The author in his preface feels that there is not as much need for a book discussing "which serologic test is better or poorer than the other" as there is for consideration of the principles of serology. 4, Conflicting serologic tests and, 5, false positive serologic tests. These points are well covered. Unfortunately for the uninitiated the Kahn verification test is spoken of freely (pp. 90, 91, 92, 93, 94, 95, 96, 97), but what the test is and what it means is not described until p. 166. 6, Serologic relapse in treated cases. This problem is not dealt with. 7, When to take the serologic tests (relation to exposure, treatment, series for deter-

mination of cure and so forth). This subject is discussed along rather broad lines; there is no guide for the practitioner not equipped with the best serologic service such as Dr. Kahn gives his colleagues. 8, Questions on cord blood tests. This is only discussed in connection with the quantitative procedure (p. 139). 9, Questions on provocative tests. No discussion. 10, Frequency of various results. 11, Number of tests necessary for various diagnoses. These questions are difficult for the expert and Dr. Kahn has handled the results of various serologic conferences expertly. The practitioner still wishes to know which test shall be believed, if so many factors affect their outcome on identical specimens in the hands of the best serologists. From these observations and other data from the text, one concludes that the subject is handled from the laboratory and not clinical viewpoint.

There are a number of commendable features in Dr. Kahn's book. The historical chapters (V and VI) on complement fixation and precipitation in syphilis are written in a fascinating style, and the chapters appended are of value for the industrial or public health physician. Dr. Kahn has clearly indicated the vast difference in a small fraction of a per cent of specificity as contrasted with a relatively large difference in sensitivity now that large population groups are being tested for syphilis. There are few errors in typography or editing. Certain ambiguous phrases like "mixed cases of syphilis" are confusing.

On the whole this book is stimulating reading for those interested in serology in syphilis control.

H. B.

THE BIOLOGY OF THE NEGRO. By JULIAN HERMAN LEWIS, PH.D., M.D., Associate Professor of Pathology, University of Chicago; Member of the Otho S. A. Sprague Memorial Institute for Medical Research; Senior Attending Pathologist, Provident Hospital, Chicago, Ill. Pp. 433; 17 tables. Chicago: The University of Chicago Press, 1942. Price, \$5.00.

The scope and method of approach of this pioneer and valuable study is well indicated in the advertisement on the cover as follows:

"The reaction to disease is no less a racial characteristic than is head form or skin color. To prove this Dr. Lewis adopts the technics of the anatomist, physiologist, chemist, and pathologist to discover many striking racially specific characteristics in the Negro's reaction to disease. Here he assembles for the first time the voluminous but widely dispersed information on the physical and biological makeup of Negroes—American and African—and on their reaction to disease. In no other people is it possible to compare simultaneously such a wide diversity of factors; they may be studied under primitive and civilized conditions, enslaved and free, comparatively pure and mixed with other races. When a balance is struck between the assets and liabilities of the Negro in his struggle with his environment, which includes disease, it is found to be in his favor. This is expressed in his ability not only to survive but to flourish on two continents.

"Differentiating between biological and environmental factors in disease, the author examines the greatest liabilities of the Negro—his excessive morbidity and mortality rates from heart disease, tuberculosis, and syphilis. Dr. Lewis suggests that the two last-mentioned diseases are more virulent in Negroes because they (*i. e.*, the diseases) are four hundred or more years younger in them than in white people. The Negro's assets are his birth rate, his physical stamina, and his resistance to malaria, exanthemata, and certain surgical conditions.

"The book will be of value to anthropologists and biologists as a measure of the differences and similarities other than the obvious ones which may exist between races. It is of interest to sociologists in pointing out the reciprocal influence of disease and social conditions. It is important to doctors as a comparison of disease behavior among races."

The book maintains the usual high standard of works from this press, both in content and format. One is surprised, however, to see on the first page Japanese names retained as co-publishers of a book that appears on May 12, 1942.

E. K.

TEXTBOOK OF MEDICAL TREATMENT. By Various Authors. Edited by D. M. DUNLOP, University of Edinburgh, L. S. P. DAVIDSON, University of Edinburgh, and J. W. McNEE, University of Glasgow. Pp. 1179; 26 illustrations. Second Edition. Baltimore: Williams & Wilkins Company, 1942. Price, \$8.00.

THIS book has been written by practicing physicians and members of the faculties of medicine of the Universities of Edinburgh, Glasgow and Aberdeen. It is strongly recommended to all those primarily interested in the fields of internal medicine and general practice. It is also an excellent textbook for students. It is up-to-date, clear, precise and concise yet detailed enough to include a thorough consideration of the treatment of the patient as a whole as well as that of his disease. The methods described by the authors are those "which from their personal experience they have found to be most useful." These, in general, are similar to the best accepted methods employed in this country.

C. D.

MAUDE ABBOTT, a Memoir. By H. E. MACDERMOT, M.D., F.R.C.P. (C.). Pp. 264. Frontispiece of Maude Abbott from the portrait in oils by Mrs. C. H. Eastlake. Toronto: The Macmillan Company of Canada, 1941. Price, \$2.50.

No one could have had even the briefest contact with Maude Abbott without realizing that she was, in more ways than one, a very remarkable woman. Many of these ways are portrayed with enthusiasm, sympathy and frankness in this penetrating memoir. Dr. Abbott's notable many—are allowed to fall naturally into line with her shortcomings—what human being does not have plenty?—to produce an accurate and interesting, three-dimensional view of this dynamic personality. The pure gold gleams in her triumphs over adversities, her resilient but by no means uncomplaining reactions to setbacks, and above all in her abnegating, self-obliterating, completely unselfish, year-long devotion to her invalid sister. The results of her persistent, untiring, though often unsystematic, activity are best seen in her noteworthy contributions to the knowledge of congenital heart disease, of which she was internationally recognized as the leading authority of her generation. This and her other scientific achievements, together with her creation and almost single-handed maintenance of the International Association of Medical Museums, and her noteworthy bibliography of the works of Sir William Osler, all well presented in this short memoir, are the high spots of her career. The chapter on Reminiscences and Anecdotes might well have been longer; one would like to have seen, for instance, the account of her first auto accident: she buys a secondhand Ford, to save time between the Women's Medical College and Blockley, and undaunted by lack of operator's license and knowledge of driving—a child runs across the street—in her confusion she pursues it on the sidewalk and eventually runs it down—fortunately its injuries are trivial and a Philadelphia friend who knows the magistrate saves her from a night in jail.

Dr. Abbott was a pioneer in several of women's activities in medicine, but she will be chiefly remembered by her many friends for the reasons so well given by Dr. Matthew Stewart, of Leeds: "Kindhearted and generous

to a fault, she combined a quiet simplicity of mind with great intellectual ability and an energy and enthusiasm which were at once the admiration and despair of her friends. In her long and happy life she had passed through much tribulation—she had had ‘misfortunes great and sma’, but aye a heart abune with a’”—and the memory of her joyous, vital, enthusiastic personality will ever be treasured by those of us who were privileged to be her friends.”

E. K.

NEW BOOKS

Biological Symposia. Edited by JACQUES CATTELL, Editor of The American Naturalist and American Men of Science. Pp. 322; many figures. Lancaster, Pa.: The Jaques Cattell Press, 1942. Price, \$3.25.

The Dynamic State of Body Constituents. By RUDOLF SCHOENHEIMER, Late Associate Professor of Biological Chemistry, Columbia University. Harvard University Monograph in Medicine and Public Health No. 3. Pp. 78; several figures and tables. Cambridge, Mass.: Harvard University Press, 1942. Price, \$1.75.

The Pathology of Trauma. By ALAN RICHARDS MORITZ, M.D., Professor of Legal Medicine, Harvard Medical School; Lecturer in Legal Medicine, Tufts College Medical School; Lecturer in Legal Medicine, Boston University School of Medicine; Pathologist, Mass. State Dept. of Public Safety; Associate Medical Examiner of Suffolk County. Pp. 386; 117 illustrations. Philadelphia: Lea & Febiger, 1942. Price, \$6.00.

Fundamentals of Anesthesia, An Outline. By Subcommittee on Anesthesia of National Research Council. Pp. 217; 72 illustrations. Chicago: American Medical Association Press, 1942. Price, \$2.50.

The Function of the Orgasm. By WILHELM REICH, M.D. Translated from the German Manuscript by THEODORE P. WOLFE, M.D. Pp. 368; several figures. New York: Orgone Institute Press, 1942. Price, \$3.00.

The review of the first number of the International Journal of Sex Economy and Orgone-Research, appearing in the August number of this Journal, is sufficiently applicable to this book not to require further notice of it in our reviewing columns.

The Reception of William Beaumont's Discovery in Europe. By GEORGE ROSEN, M.D. Foreword by JOHN F. FULTON, M.D. Pp. 97; frontispiece of William Beaumont. New York: Schuman's, 1941. Price, \$5.00.

Plastic Surgery of the Breast and Abdominal Wall. By MAX THOREK, M.D., LL.D., F.I.C.S., F.I.C.A. With an introduction by RUDOLF NISSEN, M.D., F.I.C.S., and a foreword by J. EASTMAN SHEEHAN, M.D., F.A.C.S. Pp. 446; 458 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$16.50.

Physical Chemistry. For Students of Biochemistry and Medicine. By EDWARD STAUNTON WEST, Ph.D., Professor of Biochemistry in the University of Oregon Medical School. Pp. 368; 32 tables, several figures. New York: The Macmillan Company, 1942. Price, \$5.75.

Nutrition and Chemical Growth in Childhood. Vol. I, Evaluation. By ICIE G. MACY, Ph.D., Director of the Research Laboratory of the Children's Fund of Michigan. Pp. 432; 66 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

Occupational Tumors and Allied Diseases. By W. C. HUEPER, M.D., Assistant Director and Principal Pathologist, Warner Institute for Therapeutic Research, New York City. Pp. 896; many figures, 3975 references, Index. Springfield, Ill.: Charles C Thomas, 1942. Price, \$8.00.

- Synopsis of Blood Diseases.* By A. PINEY, M.D., M.R.C.P., Director, Pathological Department, Royal Cancer Hospital, London; Physician, St. Mary's Hospital for Women and Children, London. Pp. 120; 4 plates, and several tables. Philadelphia: The Blakiston Company, 1942. Price, \$2.75.
- Blood Grouping Technic.* By FRITZ SCHIFF, M.D., Late Chief of the Department of Bacteriology, Beth Israel Hospital, New York, and WILLIAM C. BOYD, Ph.D., Associate Professor of Biochemistry, Boston University. Pp. 248; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, \$5.00.
- Symposium on Industrial Medicine.* Medical Clinics of North America, No. 4, July, 1942. Philadelphia: W. B. Saunders Company. Pp. 348; many illustrations.
- The Surgery of Pancreatic Tumors.* By ALEXANDER BRUNSCHWIG, M.S., M.D., F.A.C.S., Professor of Surgery, University of Chicago. Pp. 421; 123 figures. St. Louis: C. V. Mosby Company, 1942. Price, \$7.50.
- How to Live in the Tropics.* By VIRGINIA HUN. Pp. 178; several tables. New York: Harcourt, Brace & Co., 1942. Price, \$2.00.

NEW EDITIONS

- Essentials of Pathology.* By LAWRENCE W. SMITH, M.D., Professor of Pathology, Temple University School of Medicine; Formerly Assistant Professor of Pathology, Harvard Medical College; and Associate Professor of Pathology, Cornell University School of Medicine, and EDWIN S. GAULT, M.D., Associate Professor of Pathology, Temple University School of Medicine. Foreword by JAMES EWING, M.D., Memorial Hospital, New York City. Pp. 960; 685 illustrations. Second edition. New York: D. Appleton-Century, 1942. Price, \$10.00.
- Red Cross Home Nursing.* By LONA L. TROTT, R.N., B.S., Assistant Director, Health Education, Red Cross Nursing Service. Pp. 431; many illustrations and figures. New Edition. Philadelphia, The Blakiston Company, 1942. Price, \$.75.
- Diseases and Injuries of the Larynx.* By CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-esophagology, Temple University, Philadelphia, and CHEVALIER L. JACKSON, A.B., M.D., M.Sc. (Med.), F.A.C.S., Professor of Broncho-esophagology, Temple University. Pp. 633; over 200 illustrations including 11 plates in color. Second Edition. New York: The Macmillan Company, 1942. Price, \$8.00.
- Intestinal Obstruction.* By OWEN H. WANGENSTEEN, B.A., M.D., Ph.D., Professor of Surgery of the University of Minnesota and Surgeon-in-Chief of the University of Minnesota Hospital. Pp. 484; 143 figures. Second Edition. Springfield, Ill.: Charles C Thomas, 1942. Price, \$7.00.
- Questions in Laboratory Methods.* By R. B. H. GRADWOHL, M.D., Sc.D., Director, the Gradwohl School of Laboratory Technique, St. Louis, Mo. Pp. 71. Second Edition. Published, The Gradwohl School of Laboratory Technique, 1942. Price, \$2.50.
- Physical Signs in Clinical Surgery.* By HAMILTON BAILEY, F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Surgeon, Italian Hospital. Pp. 336; 455 figures, many in color. Eighth Edition, revised. Baltimore: Williams & Wilkins Company, 1942. Price, \$7.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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OWING to prior claims of war work, it has not been possible to complete the Progress Report arranged for this number, but it is hoped that it will appear later.

E. G. D. MURRAY.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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IMMUNITY TO POLIOMYELITIS.

HETEROLOGOUS STRAINS AND DISCREPANT NEUTRALIZATION TESTS.

EARLY in the study of poliomyelitis, the rarity of second attacks was attributed to immunity resulting from exposure to the virus. When the disease was transmitted experimentally, verification was prompt in the finding that recovered animals were refractory to reinoculation and in the discovery of neutralizing antibodies in the blood serum of previously infected persons and animals. Other general epidemiologic features placed poliomyelitis in the group of widespread immunizing infections of childhood, and thus implied subclinical infections with the virus in addition to recognized cases.

The basic evidence for subclinical infection lies in observations which indicate an unbroken gradation from frank paralytic cases, through milder and non-paralytic forms—frequently missed—to suspected

abortive infections not amenable to certain diagnosis; as well as in time and space relationships between recognized cases, implying intervening milder infections or healthy carriers; and in the occurrence of extensive immunity in the general population, as shown by virus neutralization tests. And at the present time, the concept of widespread dissemination of the virus is being substantiated by new procedures for its actual detection, not only in recognizable cases but in suspected illnesses and healthy individuals as well.

The validity of any epidemiologic inference in regard to the manner and extent of virus dissemination is largely dependent upon the correctness of the idea of subclinical infection. Thus, epidemiologic considerations restricted to the point of view that the paralytic disease is directly and completely expressive of the distribution of the virus would lead to inferences very different from those derived from studies including subclinical infections.

Because much of the evidence has been indirect, the epidemiologic concept of widespread subclinical immunization originating in older observations has been subjected to many checks and challenges. During the earlier years of investigation, because of technical difficulties, few laboratories maintained strains of virus or carried out detailed immunity studies. Thus, no very exact knowledge existed as to the momentary immunity status of individuals or communities. Nevertheless, laboratory experience and such end-point findings as the fact that, in general, individuals who had passed through an attack of the disease possessed neutralizing substance and that the blood serum of a high percentage of adults in various parts of the world had neutralizing power gave an indication of general trends in immunity, both as a result of recognized disease and as an indication of subclinical infection.

Up to this point, there had been no particular suggestion of immunologically distinct strains of virus. In the conduct of immunity tests, the only reading exacted had been whether or not a given serum neutralized "the virus" (usually an old laboratory strain). For example, in 1932, comparative tests on serum and virus obtained in widely separated localities—recent convalescent serum from Rabaul, New Britain, and pooled convalescent serum from Massachusetts, against strains of virus obtained in Australia and Vermont—revealed no immunologic differences (Table 1).*

TABLE 1.—NEUTRALIZATION OF POLIOMYELITIS VIRUS SERUM AND VIRUS FROM WIDELY SEPARATED SOURCES.

	Recent human convalescent, Rabaul 1.	Pooled human convalescent, Rabaul 2.	Pooled human convalescent, Mass.	Normal monkey.
Date inoculated . . .	11-18-32	11-18-32	11-18-32	11-18-32
American virus Aycock-Vermont . . .	Not paralyzed Neutralized	Paralysis 11-28-32	Not paralyzed Neutralized	Paralyzed 11-25-32
Australian virus Victoria NSW . . .	Not paralyzed Neutralized	Paralysis 11-28-32	Not paralyzed Neutralized	Paralyzed 11-27-32

* These studies were supported by the Harvard Infantile Paralysis Commission and by a grant from the Commonwealth Fund.

In a number of studies relating to individual cases or outbreaks, it has been found that patients in the earliest days of the disease may already neutralize virus, while others fail to do so after convalescence. Comparative neutralization tests were carried out by Paul and Trask²² on convalescent sera from paralytic cases, using a recently isolated human strain and a passage strain of virus. Five of the 6 sera taken $1\frac{1}{2}$ to 10 weeks after onset neutralized the human strain; 1 failed and still failed to do so a year later. With the passage strain, $1\frac{1}{2}$ to 10 weeks after onset, only 1 serum of the 6 tested neutralized; this 1 serum again neutralized a year later. Two of the sera which had failed to neutralize again failed a year later.

Jungeblut¹⁷ obtained neutralization in only 15 of 26 (57.6%) of convalescent sera tested against a passage strain of virus. Harmon and his co-workers¹³ tested sera from 14 patients, and found that 12 already contained neutralizing substance early after the onset of the disease.

Brodie, Fischer and Stillerman⁵ carried out neutralization tests on sera obtained during an outbreak in New York in 1935. Fourteen of 82 sera (17%) taken in the first week of the disease already neutralized a passage strain of virus. Of the 68 patients who failed to neutralize during the acute stage, 39 were retested some months later and 37 still failed. When tests were performed with a strain isolated during the outbreak, similar results were obtained. In general, patients who failed to neutralize the passage strain likewise failed to neutralize the human strain.

Hammon and Izumi,¹² using the Lansing strain and mouse neutralization, tested acute and convalescent sera from 23 patients with poliomyelitis from 3 separate outbreaks in California and Washington. The early blood of 11 showed no protection, and 9 of these developed antibodies in 16 to 29 days after onset; 2 did not change. Another group of 11 individuals, composed principally of non-paralytic cases, showed strong protection at the time of both bleedings.

Burnet and Jackson⁶ tested the antibody content of sera from 14 poliomyelitis patients in the Victorian epidemic of 1937 against the "M. V." Rockefeller Institute strain, and found that 5 neutralized at the time of acute illness. Of the remaining 9 patients, 8 still failed to neutralize when convalescent. Similar results were obtained when neutralization tests were performed on a smaller number of sera against a local virus. These investigators therefore concluded that "poliomyelitis antibody is not a result of exposure to or infection by the virus of epidemic poliomyelitis."

Such discrepant findings, even after making allowance for discordant results in about 1 test in 6, inherent in the technique of the neutralization test as ordinarily performed,^{16 25} have been enough to bring into question the specificity of neutralization found in individuals not known to have passed through an attack of the disease, and indeed have raised the question as to whether even the frank disease is to be regarded as an immunizing infection. But in more recent years, a number of laboratories taking up the study of poliomyelitis and emphasizing virus detection have added numerous strains to the few formerly employed in experimentation, and comparative studies have revealed

the existence of immunologic differences in strains of virus which had not been previously suspected.

Burnet and Macnamara⁷ found immunologic differences between a virus recently isolated from a fatal human case in Melbourne, Australia, and the Rockefeller Institute M. V. strain. In 3 instances, monkeys contracted a fatal attack of poliomyelitis following intracerebral inoculation of the M. V. strain, despite the fact that some weeks previously they had sustained a typical attack of the disease produced by the human strain. The reverse was also demonstrated in a single instance, in which a recovered monkey, partially paralyzed by the M. V. strain, was subsequently brought down with complete paralysis by inoculation with the local virus. Furthermore, it was found in neutralization tests that, although pooled convalescent serum would neutralize both strains, a few tests with individual samples of recent convalescent sera failed to show this parallelism, in that only the local virus was neutralized.

Paul and Trask²² found that the experimental disease in the monkey induced by 2 human strains failed to immunize against a subsequent reinfection by the M passage strain; and the reverse also was observed.

What with a strong preference for the parasite as a major factor in the genesis of epidemics—"epidemic strains," "importation of new strains," "increase in virulence by rapid passage," "termination of epidemics by exhaustion of susceptibles"—there had been a natural hesitancy to assume that more than one etiologic agent (immunologically different strains) might be involved in the same epidemic. Under the broader concept that environmental factors or host factors may be equally important determinants in epidemics in certain diseases, it may be seen that a number of strains of virus may be involved in the same outbreak, and this would perhaps be especially true in diseases whose viruses are more or less in continuous circulation through latent or subclinical infections. Thus, an epidemic precipitated primarily by environmental or host factors, on a background of subclinical dissemination of the virus, might contain cases due to a number of strains of virus which were in dissemination in the population at the time.

Following the discovery by Smith, Andrewes and Laidlaw²⁸ of what is now termed influenza A virus, numerous workers have agreed that this agent was responsible for many cases of epidemic influenza. Francis⁹ found an epidemic of the disease which could not be shown to have been caused by this virus. Subsequently, Stuart-Harris, Smith and Andrewes,³⁰ as well as Rickard, Lennette and Horsfall,²⁴ demonstrated that only a certain proportion of cases studied in localized epidemics were due to this agent. Their report made it evident that epidemic influenza was not due to a single etiologic entity, and indicated that at least two distinct causal agents were capable of producing the disease.

Lennette, Rickard, Hirst and Horsfall²¹ have shown that in one epidemic of influenza, even in a single institution, one or more of at least three distinct strains of influenza virus may be involved.

Howitt¹⁴ first called attention to antibodies to both Western equine and St. Louis encephalitis viruses in the blood of certain patients in California. More recently, Hammon¹⁰ and Hammon and Howitt¹¹ pointed out that human infections apparently due to both viruses were

occurring during the same epidemic, and possibly even simultaneously in the same individual.

In poliomyelitis, it has been a common observation in epidemic years that a number of cases occur in sizable population groups in individuals just arrived from distant epidemic areas, and who must have acquired their infection in the distant areas, as judged by time and place relationships. In recent years, clear-cut introductions of virus into Boston in this manner have been seen from epidemics in Illinois, 1936; Toronto, Ontario, 1937; Charleston, S. C., 1939; and Frederickton, N. B., 1941.

Kessel and Stimpert¹⁸ inoculated monkeys recovered from paralytic attacks of poliomyelitis induced by 6 strains of virus, with homologous and heterologous strains. A greater degree of immunity was observed to homologous than to heterologous strains. Several of the strains were recently isolated from cases in Los Angeles. Differences in reciprocal immunity were just as great between these recently isolated strains as between old laboratory and recently isolated strains.

Thus, it may now be seen that, because of the difficulty of establishing the epidemiologic identity of a given group of cases, or a given strain of virus, the divergent results in neutralization tests which have cast doubt on the whole phenomenon of immunity in poliomyelitis could be due to immunity tests with strains not identical with those responsible for the cases being tested.

TABLE 2.—NORMAL ADULT SERUM—NEUTRALIZATION OF DIFFERENT STRAINS OF VIRUS.

Normal serum.	Virus.	Number of sera.	% neutralized.
Chicago—adults and convalescents ^{14a}	PMV	10	100.0
		(pooled)	
Liberia—adults ^{15b}	PMV	20	90.0
Urban—adults and children, Boston, Mass. ^{3a}	Aycock	46	69.6
Rural—adults and children, Cape Cod, Mass. 4 Vermont ^{3a}	Aycock	29	20.7
Southern—adults, Atlanta, Ga. ^{3b}	Aycock	21	85.7
Mothers and newborn, Massachusetts ^{3c}	Aycock	24	83.3
			1 partial
Puerto Rico—adults ²⁹	Not stated	8	100.0
Chicago, rural Illinois; Winnipeg and Virgin Islands—adults ²⁷	Aycock	10	90.0
Samoa—adults and children ^{1a}	Aycock	27	96.3
			3 partial
Fiji—adults ^{1a}	Aycock	25	100.0
			1 partial
Fiji—adults ^{1a}	Australian	5	100.0
			1 partial
Nashville, Tenn.—adults ¹⁶	Not stated	25	84.0
China—adults ¹⁷	Not stated	12	91.7
Greenland—adults ¹⁷	Not stated	3	100.0
New York City—adults ¹⁷	Not stated	30	56.7
New York City—adults ²¹	Not stated	9	66.6
San Francisco ²⁶	Aycock	32	56.2
Montreal ⁴	Not stated	28	78.6
Sevenoaks and London, England—conv., contacts and normal children ⁸	Fl. M.	10	80.0
France ²²	Vienna, 1909	15	86.7
Bedford and Burlington, Mass.—children ¹⁵	Aycock	77	55.8

No large-scale comparative neutralization tests with normal adult serum against different strains of virus have been reported. But the fact that adult serum neutralizes the virus with the same high frequency in tests which have been performed over a period of years in many parts of the world, and with a number of strains of virus obtained in the same or in different areas can probably best be interpreted as an indication that immunologically different strains are all in equally free circulation, and that the end-point of immunity represented by normal adult serum neutralization is indicative of a very general exposure to the several immunologically different strains. The uniformity with which normal adult serum neutralizes various strains of virus is indicated in the tabulation of the results of a number of studies in the literature (Table 2).

An ideal situation for studying the development of immunity more immediately following infection would be afforded by an outbreak beginning after the importation of a single case into an isolated and previously uninfected locality. But such an opportunity is seldom presented to the epidemiologist. Under actual conditions, it is practically impossible to determine whether a given case is the first occurrence of the disease, or to group those cases which are etiologically related. Multiple cases in families present, perhaps, the nearest approach to a grouping of epidemiologically related cases, since they comprise self-contained groups from which many of the variables which might enter into other groups of cases can be excluded. When two or more cases of poliomyelitis occur in the same family simultaneously, many epidemiologic factors can be assumed to be the same. It is most likely, for example, that they are the result of exposure to a single strain of virus.

Chapin's classic studies of familial aggregation in measles, diphtheria and scarlet fever vastly elucidated the basic laws governing the dissemination of these infectious agents and the development of immunity following exposure to them. These viruses, under the conditions of exposure in a family, when introduced, tend to spread through the household—high secondary attack rate in susceptibles in measles and high harborage of *B. diphtheriæ* with or without symptoms—revealing spread through families with clinical or subclinical infection in the non-immunes.

Studies of certain features of the distribution of multiple cases in families of poliomyelitis, scarlet fever and measles² are indicative of equally extensive spread of all these infections among the members of the family and suggest that the frequency of a clinical manifestation is determined more by other factors than by exposure to the virus *per se*. In measles, it is clear that the determinant is immunity from previous infection, for the occurrence of the disease is restricted to those whose histories indicate no previous infection, and in these non-immune members of the family the attack rate is high. It seems clear likewise that, since the average immunity level as indicated by neutralization tests in poliomyelitis corresponds to that of measles, other factors are major determinants of the clinical disease upon exposure in non-immune family members.

That family saturation, upon introduction of poliomyelitis virus, assumes proportions of the order of measles has recently been verified

by Langmuir²⁰ in the detection of the virus not only in paralytic, non-paralytic and suspected abortive cases, but in well members of families as well. Thus, it becomes clear that the termination of a family outbreak can be ascribed to "exhaustion of susceptibles."

That exhaustion of susceptibles does not play the same rôle in terminating outbreaks in the community is suggested by the fact that it can be figured from the intervals between outbreaks of measles in the same population group, and the age at which the disease occurs, that the average person with measles has escaped infection in at least one previous outbreak of the disease in the community where he has lived. However, the diminution of the proportion of susceptibles in a population to a point below the threshold necessary for continued transmission to susceptibles must still be recognized as a factor in the termination of epidemics. It would be expected, because of the many more interruptions in lines of contact transmission in community outbreaks than in self-contained groups of individuals like families, that a considerably less extensive reduction in susceptibles would be equally effective in terminating community outbreaks.

Aggregations of individuals in which the conditions of dissemination more nearly approach those of a family are seen in such institutions as boarding schools.

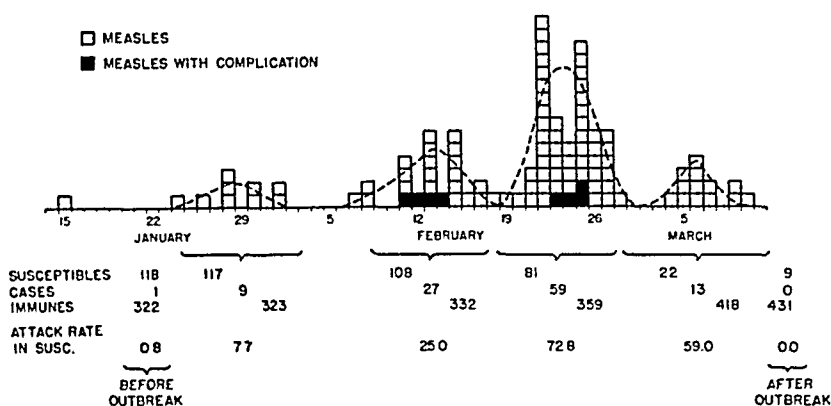


CHART 1.—Institutional outbreak of measles 1934. Four waves of secondary cases, 8 cases with complications. Showing practical exhaustion of susceptibles.

An outbreak of measles occurred in such a school in New England with a student population of 400 boys 13 to 18 years of age. In this particular year (1934), the school reopened after the Christmas vacation on January 11, and 4 days later measles developed in one of the boys who returned. Nine days later, a second case occurred. Within 8 weeks of the first case, 108 (91.3%) of the 118 susceptibles had contracted measles; and of these, 6 developed otitis media, 1 pneumonia, and 1 pansinusitis. As shown in Chart 1, the outbreak comprised four waves of cases at intervals consistent with the incubation period of measles. The attack rate in susceptibles increased with each succeeding wave in the face of decreasing numbers of susceptibles until the fourth wave, when the susceptibles had decreased to a relatively small number, and the attack rate again declined. Finally, when there were 13 cases

as sources of infection, but only 9 remaining susceptibles scattered in the population of 440 boys, no further case occurred.

In a smaller boarding school, with a student population of 190 boys of the same ages, 62 (32.6%) were susceptible according to their histories. On February 4, 1935, a case of measles occurred in the school. Within 4 weeks, 54 of the 62 susceptible individuals had contracted the infection, and complications had ensued in 3 of them. In this smaller school, the outbreak—practical exhaustion of susceptibles—took place in two discernible waves of cases at intervals corresponding to the incubation period of the disease (Chart 2).

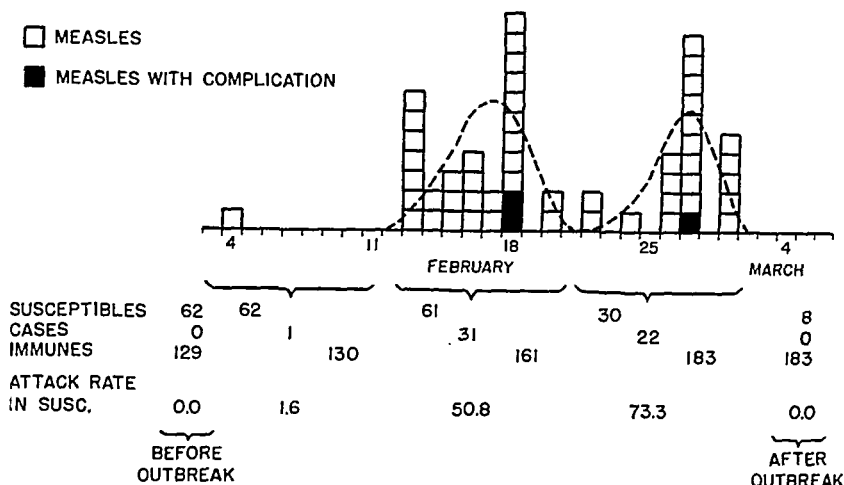


CHART 2.—Institutional outbreak of measles 1935. Two waves of secondary cases, 3 cases with complications. Showing practical exhaustion of susceptibles.

From the equally high attack rate in susceptibles in these school outbreaks, it is seen that the extent of virus dissemination is of the same order as in family outbreaks, but the rate of saturation is somewhat slower. In families, the vast majority of cases subsequent to the primary occurrence are either co-primary or secondary, with relatively few cases which are tertiary. In other words, family saturation is prompt, accomplished for the most part by a single, practically simultaneous transfer of the virus from the primary case to the remaining members of the family and requiring less than 3 weeks for completion. In the outbreak in the larger school, equally extensive saturation required four transfers and extended over 8 weeks; while in the smaller school, there were only two secondary waves in 4 weeks. Thus, in respect to rate of dissemination, the smaller school appears to lie midway between the larger school and single families.

The sequential development of the cases in these school outbreaks in groups, in accordance with the incubation period with reference to the initial case, is evidence that this primary occurrence represents the only introduction of the virus into the school population, and that therefore all the cases were etiologically identical.

Institutional outbreaks of measles, such as those just described, are commonplace occurrences, but institutional outbreaks of poliomyelitis are regarded as a rarity. Many of the older texts have pointed out that "the disease does not spread in institutions." Two reasons for this impression are apparent. In the first place, many of the institutions furnishing outbreaks of infectious diseases of childhood, such as schools, are closed during the summer months, the season of prevalence of poliomyelitis. In the second place, the number of cases of recognizable poliomyelitis which would even be expected to occur in an institution under a like impact of infection as in measles, by analogy with the incidence of the frank disease in those infected in the general population, would be small. Thus, groups of cases occurring in institutions have not been classed as outbreaks. In aggregations of young people during the poliomyelitis season, such as summer camps, the occurrence of small groups—2, 3, or 4 cases of clinical poliomyelitis—is not a rarity, and the same is true of schools opening before the end of the poliomyelitis season. Thus, when the preponderance of subclinical infections over clinical cases is borne in mind, it can be seen that these smaller groups of cases of poliomyelitis might well represent epidemiologic phenomena of the same significance as institutional outbreaks of measles. For example, if, to illustrate the point, it can be imagined that ordinary measles is subclinical and only the mastoids following measles could be considered clinical disease, then the outbreak of measles in the larger school referred to in this paper might well be analogous to institutional outbreaks of poliomyelitis comprising small groups of cases of clinical disease.

In May 1936, there occurred in the smaller of these two schools an outbreak of poliomyelitis. Within a period of 17 days, 6 paralytic cases developed. In addition, 12 non-paralytic cases were detected—cases with meningeal involvement and spinal fluid changes but no paralysis. The further extent of the distribution of the virus in the school population is not known. Unlike the two school outbreaks of measles, the poliomyelitis outbreak cannot be attributed to a recognized single earlier case. Actually, 5 paralytic cases and 5 non-paralytic cases occurred within a space of time short enough to suggest that they were common source infections from a single previous but unrecognized case in the school. No common exposure outside the school could be established for this group of cases. At any rate, the suggestion here, as in the two school outbreaks of measles, is to the effect that in all probability the poliomyelitis outbreak was the result of a single introduction of the virus into the school and that the cases in the outbreak were etiologically identical.

In Chart 3 are shown the distribution in point of time of the paralytic cases and the non-paralytic cases which came to diagnosis; in dotted lines, the presumed initial subclinical infection; and two presumed waves of subclinical infection at incubation period intervals. Although such subclinical infection was not actually established, as by virus detection or immunity tests done later, the probable dissemination of the virus in the school has been reconstructed on the basis of evidence indicating widespread subclinical infection in the long run in the population in general and within a household upon introduction of the virus and by analogy with the more apparent widespread dissemination of measles within households and schools.

Under this sort of reconstruction the distribution of recognized poliomyelitis, more particularly paralytic cases, gives the appearance of being the epidemiologic analogue of the complications seen in the measles outbreak in the school, a view not inconsistent with available knowledge in general that the virus is widespread and that the paralytic disease is the exceptional "complication" of virus infection. That the dissemination of the virus through the members of the school was fairly prompt and, therefore, presumably extensive is suggested by the fact that promptly upon the occurrence of the first cases about half the members of the school left for their homes, but following the exodus from the school the subsequent attack rates were the same in those who had left the school for their scattered homes as in those who remained at the school.

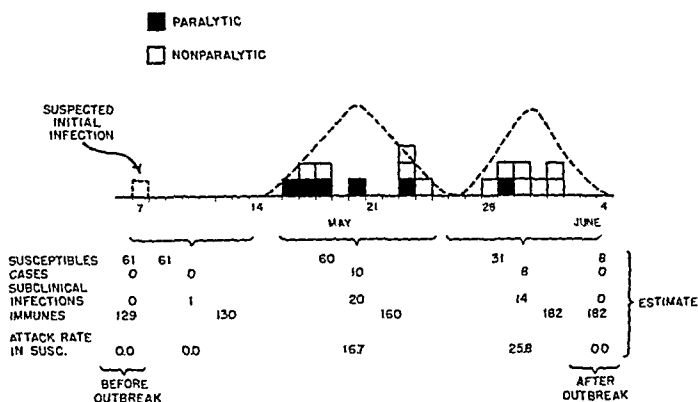


CHART 3.—Institutional outbreak of poliomyelitis 1936. Six paralytic and 12 non-paralytic cases with estimated waves of secondary subclinical infections and exhaustion of susceptibles.

As indicated on Chart 3 in dotted lines, the reconstructed outbreak of dissemination of the virus begins with a presumed subclinical infection occurring around May 7. As is generally true of outbreaks of poliomyelitis, no clear-cut introduction of the virus into the school was traced, but the following circumstances at least might be considered as possibilities in this connection.

In the first place, the incidence of poliomyelitis in Massachusetts in the month preceding the outbreak in the boarding school—the season of lowest ebb of the disease in this state—was relatively high as compared with the corresponding 4-week periods in other years (Table 3).

TABLE 3.—POLIOMYELITIS IN MASSACHUSETTS

4 weeks ending.	No. of cases.	4 weeks ending.	No. of cases.
5-16-31	2	5-22-37	1
5-21-32	1	5-21-38	0
5-20-33	1	5-20-39	1
5-19-34	2	5-18-40	1
5-18-35	2	5-17-41	0
5-16-36	5	5-16-42	1

Eleven cases were reported from widely scattered areas in the state in the month preceding the school outbreak and during the period of the outbreak. It was established that there was no direct contact between any of these outside cases and the cases in the school, but a number of instances of possible indirect contact between widely separated cases and the school were found.

A deliveryman making regular calls in Attleboro and Wellesley, where cases were reported April 14 and 28, as well as in other towns, also made deliveries to the school.

On April 15, O. K., a 16-year old boy, left home without parental consent, hitch-hiked to a neighboring state and returned to his home by way of Boston during the week preceding the onset of his disease April 27, and spent whole days at the movies, in stores and restaurants in his home city—a few miles from the school. He spent the evening of April 28 (with beginning symptoms) with a close friend, B. D., who played in an orchestra at an amusement park a few miles from the school.

On May 1, Mr. LaB., who owned a drugstore in the village, where the school was located and where the students gathered, visited the amusement park where B. D. was playing in the orchestra. Such circuitous lines of contact between recognized cases of poliomyelitis are for the most part all that can be seen in the usual investigation and indeed all that are to be expected considering the evident preponderance of subclinical over clinical infections.

No immunity tests were carried out at the time of the school outbreak, but 12 months later 10 tests on blood serum from 7 of the recovered cases, paralytic and non-paralytic, against an old laboratory strain (Aycock strain recovered in 1921), gave a positive neutralization in only 3 out of 10 tests. At this point, it might have been concluded with Burnet and Jackson that "poliomyelitis antibody is not a result of exposure to or infection by the virus of epidemic poliomyelitis." But from the one fatal case in the school outbreak a strain of virus had been obtained and at the time neutralization tests were run against the old laboratory strain, tests were also carried out against the local strain. In all of 10 tests on 7 of the cases who had passed through the school outbreak—3 paralytic and 4 non-paralytic—the virus from the school outbreak was neutralized (Table 4).

TABLE 4.—NEUTRALIZATION TESTS.

H. C. S. (H. virus).		Virus.	
		H.	A.
P. A.	NP	+	—
P. A.	NP	+	—
C.	P	+	—
R.	NP	+	—
R.	NP	+	—
N.	P	+	—
P.		+	—
T.	P	+	±?
T.	P	+	+
V. H.	NP	+	+

Fragments of spinal cord from the one fatal case in the school outbreak (H strain) readily produced poliomyelitis in normal Rhesus

monkeys with serial passage. Furthermore, this strain of virus produced a second attack of paralytic poliomyelitis with additional paralysis in 3 monkeys recovered with residual paralysis from an attack of poliomyelitis induced by inoculation of the Aycock strain. Two monkeys convalescent from attacks produced by the H strain and 3 monkeys recovered from attacks induced by both the Aycock and the H strains were available for subsequent neutralization tests against the strain obtained in the school outbreak, the Aycock strain, the J strain (which had recently been obtained from a patient developing the disease in Boston upon arrival from Illinois in 1936), and a strain obtained from the late Dr. James D. Trask.

TABLE 5.—NEUTRALIZATION TEST—CONVALESCENT MONKEY SERUM (VIRUS H AND A VIRUS) AGAINST H, A, AND TWO OTHER VIRUSES.

Convalescent monkey serum.	Virus.			
	H.	A.	J.	T.
Virus H 1397	+	±		—
H 1397	+	—		
H 1397	+	—		
H 1493	+	+		
A & H 1215	+	+		
A & H 1215	+	+		
A & H 1215	+	+	+	—
A & H 1081	+	±	+	—
A & H 1287	±	—	+	—
A & H 1287	±	±		
A & H 1287	—	—		

As shown in Table 5, monkeys that had recovered from the H virus regularly neutralized this virus and failed to neutralize the Aycock or the Trask (T) virus. Monkeys recovered from attacks induced by both the Aycock (A) and H strains neutralized both these strains of virus as well as the J strain. Four animals, 1 recovered from an attack from the H virus and 3 recovered from attacks from the H virus and the Aycock virus, all failed to neutralize the Trask virus.

These cross-immunity tests clearly reveal immunologic differences between these strains of virus and in turn serve to explain the failure of convalescent patients in the school outbreak to neutralize the old laboratory Aycock strain of virus.

In summary, it may be pointed out that discrepant neutralization tests in poliomyelitis (which have in the past been interpreted as indicating that on the one hand immunity, as shown by the neutralization test, is not indicative of protection against infection with the virus, and on the other hand does not follow infection with the virus) appear to be due to the use of heterologous strains of virus.

Where human convalescent sera from cases occurring in an outbreak in which the epidemiologic evidence indicated infection with a single strain of virus were tested against that strain, neutralizing antibody was regularly found; while in tests against an old laboratory strain, only a portion had neutralizing antibody.

Monkeys convalescent from an attack from each of two strains of virus neutralized the homologous virus but not the heterologous strain. Monkeys convalescent from separate attacks from the two strains of virus neutralized both strains.

Normal adult serum from many parts of the world all neutralize a number of strains of virus with equally high frequency.

It is suggested that the momentary immunity status of individuals is represented by the presence of neutralizing antibody to strains to which the individual has been exposed previously; and the end-point of immunity (adult) by the presence of neutralizing antibody to a number of strains.

It, therefore, would appear that the several strains of virus are all in equally free circulation and attain an equally widespread dissemination; furthermore, there are indications that a given outbreak may not be caused primarily by the introduction of a single strain (from a single case) but may be precipitated by other factors on a background of subclinical carriage of a number of strains.

W. LLOYD AYCOCK, M.D.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, *i. e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the more exact meaning.

THE EDITOR.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

OCTOBER, 1942

ORIGINAL ARTICLES

**THE INDICATIONS AND LIMITATIONS OF PROSTATIC SURGERY
IN THE PRESENCE OF CARDIAC DISEASE**

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SINCE patients having abnormalities of micturition resulting from disease of the prostate are usually beyond middle life, they will show a rather high incidence of cardiac disability. In some instances the cardiac and circulatory condition is one which will permit surgical intervention with safety; in others the only safe procedure is palliation of the urinary obstruction until such time as treatment of the cardiac dysfunction has restored circulatory balance.

Complete urinary retention creates a surgical emergency and its relief is a matter of immediate concern. The bladder must be drained of urine and means provided for keeping it empty. Once this has been done, subsequent operation on the obstructed vesical outlet becomes an elective procedure which may or may not be wise.

It is now generally agreed that patients having cardiac lesions often tolerate operation unexpectedly well. Indeed, the condition of the circulatory system usually improves immediately on relief of the obstructed bladder. The patient past middle life is not to be considered a poor operative risk for surgery of the prostate merely because of his years. For these reasons a proper evaluation of the factors involved when cardiac disease and urinary obstruction of prostatic origin coexist, is very important.

In studying these problems, the following classification has been made largely as a matter of convenience in discussion, because the problems of diagnosis and treatment in each differ significantly.

GROUP 1. Urinary retention developing during or after an acute cardiac crisis.

GROUP 2. Cardiac disease appearing after acute urinary retention or efforts to relieve it.

GROUP 3. Myocardial insufficiency in the presence of chronic urinary retention.

GROUP 1. The term *cardiac crisis* is intended to include some severe cases of angina pectoris, coronary thrombosis, and acute cardiac decompensation. In all three conditions it is necessary to confine the patient to bed for some time and otherwise to curtail his activities to a large extent. The weakness which accompanies these conditions and the restriction of fluid intake regarded as advantageous in treatment may be contributory factors to urinary retention. Chronic passive congestion resulting in oliguria and local edema of the pelvic viscera may also predispose to it. Besides this, urinary obstruction may appear as the result of vigorous diuretics, such as mercupurin. These may cause rapid excretion of 5 or 6 liters which makes such demands on the partially obstructed outlet of the bladder that complete retention supervenes. Or intravesical hemorrhage may occur spontaneously from the enlarged prostate and thus precipitate retention. Furthermore, the excessive use of morphia, amyl nitrite, or barbiturates tends to diminish the desire to urinate until a point is reached at which the detrusor becomes overstretched and temporarily loses adequate power to expel the contents of the bladder. Care must be taken to differentiate oliguria and true vesical retention of urine in order to avoid unnecessary catheterization.

The following 3 cases are discussed to illustrate the problems of diagnosis and treatment presented by this group of patients.

CASE 1. A merchant, aged 68, was admitted to hospital on account of cardiac decompensation and acute urinary retention. On 2 occasions during the preceding 18 months he had been treated for the same difficulties. He had been discharged from the hospital only 5 weeks earlier, after treatment for infarction of the myocardium, cardiac decompensation with pleural effusion, and urinary retention due to benign hyperplasia of the prostate. Treatment had consisted of digitalization, thoracentesis, diuresis by mercupurin and intermittent catheterization. After the acute cardiac insufficiency had been controlled and a satisfactory diuresis obtained, the patient was able to be out of bed. The blood pressure then measured 100/70 mm. Hg. Ability to empty the bladder returned gradually. After 4 weeks at home, cardiac failure recurred; and 5 days later, acute urinary retention. Constant urethral drainage at home was not tolerated, and he returned to the hospital. Thoracentesis was performed on the 1st, 10th, and 14th days in the hospital, 800 cc., 1000 cc., and 1200 cc. being removed on the respective occasions. Urethral catheterization and irrigation of the bladder was necessary three times daily. Mercupurin 1 cc. was administered intravenously on 3 occasions resulting in a urinary output of 2600 to 4400 cc. Digitalis folia 0.1 gm. was given daily. After 5 days, the patient could void spontaneously but carried a residual urine of 300 cc. For the first 10 days there was a daily rise in temperature to 101.5° but it was normal thereafter. On the 23rd day a transurethral prostatectomy was carried out under a low spinal anesthesia. Operation was performed with the patient in a semireclining position. The pulse remained at a rate of

80 per minute, respirations 22 per minute and the blood pressure measured 90/70 mm. Hg throughout the procedure. The bladder was drained by an inlying urethral catheter for 48 hours, after which the patient was able to empty it with ease. He was discharged 1 week later. At examination a month after discharge, there had been no recurrence of cardiac insufficiency or further urinary difficulty.

Here we have an example of recurrent cardiac decompensation, each episode being accompanied by progressively more severe urinary retention. From the first it was known that he had definite hyperplasia of the prostate. However, surgery was unnecessary since micturition became normal again after regaining compensation sufficiently for the patient to be allowed out of bed. At the second episode of decompensation, however, retention lasted longer and was more difficult to combat. At the third, prostatectomy or provision for permanent drainage was indicated.

The next case represents a somewhat different and less difficult problem than the foregoing, but is appropriately classed in the same group.

CASE 2. A clergyman, aged 63, was admitted 2 weeks after an acute attack of substernal pain which had lasted for 3 days. He had been ordered to bed by his local physician, but in spite of this he continued to have intermittent attacks of anginal pain. Gradually difficulty in voiding began, ending in total retention of urine necessitating catheterization. At the time of hospitalization there was no evidence of congestive failure and no evidence of cardiac abnormality was demonstrable by physical examination while the patient was at rest. The pulse was regular, 80 per minute, and the respiratory rate, 20. The blood pressure was 120/80 mm. Hg. A diagnosis of recent anterior myocardial infarction was made by aid of the electrocardiogram. The bladder could be palpated at the level of the umbilicus. The prostate was felt to be moderately enlarged on rectal examination. Upon catheterization, 1500 cc. of clear urine was obtained. Catheterization was carried out twice daily and the bladder irrigated. The non-protein nitrogen of the blood measured 35 mg.%. On the fourth day in the hospital, intravenous urograms showed prompt excretion of the opaque material from each kidney; the outlines of the renal pelvis were normal. The fluid intake was increased to 3000 cc. and the amount of urine voided increased from 500 cc. to as much as 2000 cc. in 24 hours with the aid of diuretics. However, even after being out of bed for a week there was still a residual urine of 1100 cc. on occasions. On the 8th day in the hospital, 3 weeks after his attack of coronary occlusion, cystoscopic examination was performed and obstruction of the vesical outlet by an enlarged median lobe of the prostate and moderate lateral lobe hyperplasia was seen. The next day transurethral resection of the prostate was done under low spinal anesthesia. The blood pressure remained stable at 110/80 mm. Hg during operation. The urethral catheter was removed on the 4th day after operation and the patient was able to empty his bladder completely thereafter. He was discharged from the hospital 1 week later, and has continued well 2 months after operation.

This patient presents an instance of urinary retention occurring as a complication of coronary thrombosis without myocardial insufficiency of a degree severe enough to cause acute passive congestion. Digitalization was not necessary. The patient was found

to have also vesical atonia and benign hyperplasia of the prostate, the combination of which was sufficient to produce total retention. Subsequently with improvement in his general condition he was able to empty his bladder incompletely and continued to have a large residual urine. At cystoscopic examination it was seen that the inability to void was largely due to prostatic obstruction and not to a paralysis of the bladder. Renal function was normal and no significant infection was present. It was not necessary to drain the bladder suprapubically since catheterization was well tolerated. As this patient did not suffer from orthopnea, perineal prostatectomy could have been carried out but was deemed unnecessary. Following transurethral prostatectomy 3 weeks after the coronary thrombosis no further urinary difficulty was experienced.

The next case represents still another variation in clinical course, yet it falls into the same group as the above two.

CASE 3. A man, aged 80, was admitted to the hospital on account of inability to urinate for 3 days. For 10 years he had been treated intermittently in the Out-Patient Department for hypertensive heart disease with auricular fibrillation. There had been repeated episodes of difficult micturition; and after an attack of acute urinary retention 5 years before, prostatectomy was advised but was refused. At the present admission he was dyspneic, and scattered râles were heard at the base of the lungs. The heart was enlarged to the left and its action irregular. The blood pressure was 180/110 mm. Hg. The electrocardiogram showed auricular fibrillation and an abnormal ventricular complex. The bladder was palpable halfway to the umbilicus and at cystoscopic examination benign hyperplasia of the prostate causing total retention of urine was demonstrated. Urinalysis showed a specific gravity of 1.030, very slight trace of albumin, and 5 to 10 erythrocytes in the sediment. Digitalization was instituted and the bladder placed on constant drainage by a urethral catheter. The latter was poorly tolerated and 3 days later suprapubic cystotomy was performed. Phenol-sulphonephthalein excretion was 45% the first hour and 15% the second hour. The blood urea nitrogen was measured at 31 mg. per 100 cc. The specific gravity of the urine varied from 1.008 to 1.030. In spite of digitalization and a well-established renal equilibrium after 3 weeks in the hospital the cardiac condition seemed too poor to permit prostatectomy. He was discharged from the hospital to recuperate at home while suprapubic drainage of the bladder was still being maintained. After 7 months at home, the catheter was removed. The urinary fistula healed quickly and normal micturition was resumed. There was no recurrence of urinary difficulty and he died 5 years later of bronchopneumonia. At postmortem examination, the important findings in addition to pneumonia were coronary sclerosis, cardiac hypertrophy and dilatation, benign hyperplasia of the prostate without urinary retention and a small papillary carcinoma of the rectum without metastasis.

This patient's course is described particularly to illustrate the value of conservative therapy when a serious contraindication to operation is present. The resumption of nearly normal micturition without prostatectomy is not rare in such cases. One must assume that this occurred as a result of coincident improvement of his cardiac condition, with relief of local edema and congestion of the

vesical outlet following drainage. Thus it is possible that a more accurate evaluation of every patient may permit avoiding operation for some. It is often possible to introduce the suprapubic catheter by the use of a trocar instead of subjecting the patient to the more extensive operative wound of a cystotomy.¹ This is a simple, safe procedure in a patient having a distended bladder. After improvement has taken place following drainage, the vesicle function can be tested by intermittent clamping of the suprapubic tube and allowing the patient to attempt micturition. This method of testing the patient's ability to empty the bladder is of value, particularly in those who are poor operative risks.

GROUP 2. In this group the urinary retention precedes the earliest abnormal cardiac manifestation. Many of the unexpected cardiac complications of prostatic surgery can be anticipated and possibly some prevented by a more searching investigation and longer preoperative preparation in individual instances. It is usually possible to estimate accurately the efficiency of the heart and its response to effort. This is of particular importance in elderly patients. Levine³ has pointed out that in estimating the risk which a given cardiac condition adds to that of the contemplated operation, there are two important factors to be considered. The first and most important is the ability of the heart to respond to effort. If the cardiac condition has been well compensated and the patient able to lead an active life, the heart has already given evidence of being able to withstand a greater load than any operation will demand. It must be remembered also that the peripheral circulation may fail with equal facility whether the heart is diseased or not. Thus, the history of cardiac efficiency is even more important than the physical examination; whereas a history of breathlessness or substernal pain may designate the presence of cardiac disease even though physical examination is not remarkable. Such symptoms are more informing than the presence of a murmur or of cardiac hypertrophy.

The second important factor is the liability of the heart to the so-called "accidents" of heart disease. These unpredictable complications which may suddenly change the prognosis are acute coronary thrombosis, embolism, Adams-Stokes attacks, paroxysmal tachycardia, auricular fibrillation, bacterial endocarditis, and ventricular fibrillation. Fortunately, such postoperative complications are not common. Though it is impossible to foretell events in individual instances, one can classify all cases into those that are more and those that are less likely to develop these complications. Since prostatectomy is never an emergency operation, in this field of surgery particularly, it is possible and important to delay intervention in those patients who are more likely to develop one of the accidents of cardiac disease. This period of delay is not one of temporizing, but rather one of active therapy. The most important

feature is that of vesical drainage which permits return of maximal renal function, stabilization of peripheral circulation, and increase of cardiac efficiency. The patient's exercise tolerance is carefully studied and his activities steadily increased as it improves. Vital capacity studies are helpful in judging improvement of cardiac efficiency. The day-to-day chart of the pulse, respiration, blood pressure and fluid exchange, show at a glance the degree of improvement.

The following case is illustrative of the important features mentioned above.

CASE 4. A clerk, aged 57, had his first attack of urinary retention while on a long motor trip. He stopped twice a day for 3 days to be catheterized by physicians along the way. On the 4th day of his illness he was admitted to hospital. The past history revealed that he had had nocturia 2 to 3 times each night for several years and progressive increase of urinary frequency during the past year with associated loss in force and caliber of the urinary stream. Otherwise his general condition had been good and any abnormal cardio-respiratory symptoms were specifically denied. The heart sounds were rather distant and regular at a rate of 70. The blood pressure was 150/80 mm. Hg. The lungs were clear. The liver was not palpable. The bladder was palpable at the level of the umbilicus. By rectal examination the prostate was found to be symmetrically enlarged, smooth and firm. At cystoscopic examination, hyperplasia of all lobes of the prostate was found causing total retention of urine. Culture of the urine yielded a growth of enterococci. The urine contained a slight trace of albumin and the sediment showed 10 leukocytes per high-power field. A catheter was inserted into the distended bladder via a trocar passed just above the pubis. The patient was kept on constant drainage for 10 days, being encouraged meanwhile to be active about the ward. Though the blood urea nitrogen was normal, the phenolsulphonephthalein excretion was only 10% in the first 20 minutes, and 50% in 2 hours. On the 10th day transurethral prostatectomy was performed under spinal anesthesia and the suprapubic drainage of the bladder continued as before.

Two days after operation the patient complained of pain in the right side of the chest where dullness on percussion and diminished breath sounds were found. A few hours later he had a chill following which a transitory pleuritic friction rub was heard. The right side of the chest was splinted by strapping for relief of the pain which morphia did not control. The next morning there was bloody sputum, the heart was enlarged, its action irregular, and many moist râles were heard in the lungs. A Roentgen-ray film of the chest showed a pleural effusion on the right, elevation of both diaphragms and cardiac dilatation. Rapid digitalization was instituted. An electrocardiogram showed auricular fibrillation with a ventricular rate of 150 per minute. The patient received 1.4 gm. of digitalis folia in the next 24 hours and the heart rate became regular at 50. Digitalis was discontinued after decompensation had rapidly cleared, but bloody sputum persisted for 2 weeks. Fortunately there was no renal or local operative complication; he was allowed up 13 days after operation and was discharged from the hospital 1 week later. Micturition was performed normally after removal of the suprapubic catheter on the 15th postoperative day. The patient was entirely well and returned to work a month later.

This patient had as postoperative complications pulmonary embolism, paroxysmal auricular fibrillation, cardiac dilatation and decom-

pensation. In reviewing his history after recovery he admitted having had several attacks of dyspnea, palpitation and substernal pain in the past. Being of an apprehensive nature he had preferred for the sake of his family to withhold this information. After his recovery, on physical examination the heart seemed quite normal and the electrocardiogram showed no abnormality. In retrospect it is only fair to say that the period of preoperative preparation should have been longer and the evaluation of his response to effort more searching. It seems that had an accurate history been given and digitalis used before operation, myocardial insufficiency might have been avoided. However, one cannot assume that this would have prevented the pulmonary embolus. The merits of the use of the suprapubic catheter are here demonstrated again in the face of severe circulatory complications, for any additional complications commonly caused by the indwelling urethral catheter might have been sufficient to alter the ultimate result.

GROUP 3. We consider here those patients having chronic urinary retention due to the enlarged prostate and secondary cardiac dilatation with myocardial insufficiency. In general, it may be said that so far as the cardiac disease goes, the prognosis here is better than in those who have had previous coronary disease. However, it is to be remembered that coronary thrombosis can occur in anyone having coronary artery sclerosis. The latter anatomic finding is common in the older age groups.

The patients of this group usually have severe renal damage so that the prognosis depends more upon the potential renal reserve than on any other single factor. Here we find necessary the most prolonged preoperative preparation, but as a result of this preparation, some of the most gratifying end results are obtained. It has been said^{3,4,5} that all cardiacs withstand surgery surprisingly well except for those who have nephritis, congestive failure, or coronary artery disease. The patient suffering from prostatism often has pyelonephritis and in the presence of coincident heart disease the problem of treatment becomes increasingly difficult. But by proper preoperative care, and timing of the operation the risk is greatly diminished. The period of preparation if long, need not be spent in the hospital. It may be necessary to institute drainage for several months before surgical intervention is safe. One can be certain of the best possible prognosis for the individual patient if he withholds operation a little longer than seems really necessary. The following case is illustrative of the proper management of the problems presented by this group.

CASE 5. A retired business man, aged 71, was admitted to the hospital because of frequency, dribbling and incontinence of urine for 3 months. For 3 weeks the patient had noted progressive dyspnea, orthopnea, and swelling of the feet and legs. He was found to be dehydrated and emaciated. The tongue was coated. The heart was greatly enlarged to the left,

the apical impulse being in the midaxillary line in the 6th interspace. The blood pressure measured 170/90 mm. Hg. The breath sounds were diminished at both bases and numerous moist râles were heard over both lower lobes of the lungs. A presystolic murmur was heard at the apex. There was edema of the legs extending up to the knees. The bladder was palpable just below the umbilicus. The prostate was greatly enlarged and there was a hard nodule palpable in the right lobe. The patient was digitalized and the bladder drained by the suprapubic route. After 3 days edema of the legs had cleared, the apical impulse was found in the 5th interspace just outside the nipple line, but the râles persisted in the lungs. The diastolic murmur could no longer be heard. In spite of constant drainage of the bladder the non-protein nitrogen of the blood rose from 62 mg. % to 94 mg. per 100 cc. The systolic blood pressure fell gradually from a level of 170 to 130 mm. Hg and the diastolic from 90 to 60. During the next 2 months the patient gradually improved. The vital pulmonary capacity increased from 1700 to 3200 cc. All signs of cardiac decompensation completely disappeared. The non-protein nitrogen of the blood fell to a level of 40 mg. per 100 cc. but the phenolsulphonaphthalein excretion did not exceed 35 per 100 cc. The electrocardiogram showed inversion of the T wave in all leads and an abnormal Lead IV. After 56 days of preparation a transurethral prostatectomy was performed. The tissue proved to be carcinoma of the prostate. Seven days later the suprapubic catheter was removed and normal micturition occurred thereafter. He was discharged from the hospital a week later, 70 days after admission. Three months later he returned because of lobar pneumonia; and died within 24 hours. Autopsy showed lobar pneumonia due to *B. Friedländeri* (*Klebsiella pneumoniae*) involving the entire right lung, and a blood culture positive for the same organism. There was hypertrophy (440 gm.) and dilatation of the heart and an acute pericarditis. The coronary arteries showed only a slight degree of hyaline thickening of the intima and fibrosis of the media. The carcinoma of the prostate had begun to invade the periprostatic tissue but there were no demonstrable lymph node metastases. Roentgen therapy had caused no apparent inhibition of growth of neoplastic cells. The vesical orifice presented a "cup"-like depression in the prostatic portion with a resulting ample outlet. The mucosa over the prostatic urethra was well healed. There was a mild chronic cystitis. The kidneys appeared normal and microscopic examination showed a rather slight degree of pyelonephritis (quite inactive) which in view of the past history of marked urinary retention and infection as well as poor renal function, was striking.

Such patients will always require prolonged preoperative preparation. For these the simplest immediate solution is installation of a suprapubic catheter. After drainage has been established there often follows a short period when the patient seems to be worse. Complete disorientation is common and the non-protein nitrogen of the blood increases in amount. Also during this time there is usually a noticeable drop in blood pressure which must be explained by the sudden relief of obstruction and resumption of free excretion. The transitory rise in non-protein nitrogen of the blood and varying degrees of oliguria to anuria may be explained on the basis of previous dehydration and renal vascular engorgement caused by urinary obstruction. Under the conditions imposed by urinary retention, the kidney is forced to concentrate to the limits of its ability constantly. What happens to such a kidney when all obstruction is

released, depends on a reciprocal relationship with the entire cardiovascular system. In the case above described there was a quick response of the heart to digitalis and other general measures but the kidneys were very slow to respond to treatment. Only after almost 2 months of therapy was the patient considered in a condition suitable for operation. From this, recovery was prompt, but 3 months later death occurred from pneumonia. Postmortem examination of the heart and kidneys showed conditions far closer to normal than one would have expected considering his former critical state.

Analysis of 25 Cases of Prostatism Associated with Heart Disease.

In order to gain a clearer conception of the indications for and limitations of prostatic surgery presented by patients having cardiac disease a study of the records of 25 such patients has been made. The salient features of these records is presented in Table 1. The only selection that has been used has been an effort to choose primarily patients who have been in this hospital during the last 5 years, with the majority of whom the writer has been personally familiar. Ten of the patients showed clinical evidence of coronary sclerosis and 4 of these had coronary thrombosis. There were 15 patients having the diagnosis of arteriosclerotic heart disease, without specific evidence of coronary thrombosis. Only 5 presented the anginal syndrome. There were 7 patients having definite heart failure with either acute or chronic passive congestion. In 4 instances auricular fibrillation was present, one of these instances occurring in the postoperative period.

There were 4 patients in the 6th decade, 7 in the 7th, 11 in the 8th, 2 in the 9th, and 1 in the 10th. All patients were admitted to the hospital while suffering from total retention of urine.

From a study of Table 1, it is seen that 10 patients had a systolic blood pressure of 170 mm. Hg or more at the time of admission to the hospital. Five of these maintained a definite hypertension throughout hospital stay without any significant drop in blood pressure after adequate vesical drainage had been established. These patients are regarded as having definite hypertension. One patient having arteriosclerotic heart disease and auricular fibrillation had a pressure of 125/65 mm. Hg both before and also after drainage. He returned 5 years later having a pressure of 190/100 mm. Hg. Another patient showed no diminution of hypertension after the bladder had been on drainage for 5 years. Such findings may be indicative of two things: (1) there has already been irreparable renal damage before vesical relief is obtained, and (2) a fairly good myocardium is present to maintain such a peripheral blood pressure over such a period of time without heart failure. A significant drop in blood pressure (20 mm. Hg or more) occurred in 10 patients following drainage of the bladder. This fall in blood pressure usually begins within 24 hours after relief of urinary retention. In those cases in which retention has been acute and of short

TABLE I.—AN ANALYSIS OF 25 CASES OF COEXISTING PROSTATISM AND HEART DISEASE

Case	Age	Cardiac diagnosis	Duration of urinary retention	Mg. % non-protein nitrogen of blood	Blood pressure, mm. of mercury			Days treatment before operation	Operation* T.P.	Days in hospital after operation	Result
					Initial	After drainage	At discharge				
1	68	Cor. thrombosis; card. insuff.	2 yrs.	53 37	110/76	90/60	90/60	22	T.P.	8	Improved
2	63	Cor. thrombosis	2 wks.	35	120/80	120/80	120/80	24	T.P.	10	Improved
3	57	Arteriosclerotic ht. dis.; auric. fibrill.	3 days	29 30	150/80	130/80	110/60	9	T.P.	21	Improved
4	71	Arteriosclerotic ht. dis.; card. insuff.	3 mos.	62 94 41 42	170/80	120/75	135/60	64	Cystotomy T.P.	13	Impr.; died 3 mos. later of pneu.
5	80	Cor. sclerosis; auric. fibrill.; hypertension	10 yrs.	30 46	180/110	..	210/90	..	Cystotomy	25 7 mos. drain.	Impr.; died 5 yrs. later; cbr. thrombosis
6	53	Angina pectoris; arteriosclerotic ht. dis.	1 day	45 32	130/90	115/70	110/70	15	T.P.	26	Improved
7	74	Arteriosclerotic ht. dis.; auric. fibrill.	3 mos.	28 38	125/65	130/65	135/65	74	Cystotomy T.P.	6	Improved
8	72	Arteriosclerotic ht. dis.	18 mos.	109 67 56	105/70	90/60	125/85	365	Cystotomy S.P.	27	Improved
9	79	Arteriosclerotic ht. dis.	8 yrs.	141 77	190/100	130/80	140/80	28	Cystotomy P.P.	5	Dead; renal failure
10	74	Arteriosclerotic ht. dis.	4 yrs.	28 19	155/90	105/60	110/80	23	P.P.	76	Impr.; well 5 yrs. later
11	69	Arteriosclerotic ht. dis.; myocard. insuff.	7 days	28 20	115/75	115/75	120/75	21	S.P.	13	Improved
12	81	Arteriosclerotic ht. dis.; myocard. insuff.	7 days	45 30	135/70	135/70	130/70	11	S.P.	18	Impr.; well 4 yrs. later

13	68	Arteriosclerotic ht. dis.; myocard. insuff.	2 days	25 25	190/90	160/80	180/90	30	Catheter cystoscopy	..	Impr.; well 1 yr. later
14	72	Arteriosclerotic ht. dis.; auric. fibrill. pneumonia	1 day	22	170/80	150/90	150/90	3	Transfer to medical	..	Improved
15	72	Arteriosclerotic ht. dis.	12 days	34 26	180/90	140/90	130/80	10	P.P.	30	Improved
16	76	Arteriosclerotic ht. dis.	1 yr.	38 49 60 40	125/80	130/80	110/60	57	Cystotomy S.P.	25	Improved
17	59	Hyperten. ht. dis.; myocard. insuff.	8 yrs. intermittent	95	150/110	130/80	130/80	25	Cystotomy	..	Impr.; living 3 yrs. later
18	60	Cor. sclerosis; anginal syndrome	3 years. intermittent	57	120/80	120/80	130/80	11	T. and S.P.	37	Impr.; diab. mell.
19	78	Arteriosclerotic ht. dis.	5 wks.	28 42	150/80	115/60	110/60	2	Transurethral resection; cystotomy radon	11	Died; cor. thrombosis
20	58	Cor. (old) thrombosis; angina	3 mos.	37	190/80	185/90	180/90	9	P.P.	19	Impr.; diab. mell.
21	66	Arteriosclerotic ht. dis.; angina	4 mos.	32 38 24	125/70	125/70	130/70	6	P.P.	17	Improved
22	77	Arteriosclerotic ht. dis.	10 days	32 22	115/70	110/70	110/60	16	S.P.	12	Improved
23	91	Arteriosclerotic ht. dis.; myocard. infarct.	30 days	60	140/60	..	135/80	3	T.P.	2	Dead; renal failure
24	76	Cor. sclerosis; hypertension	3 days	60 32	210/110	185/120	160/100	35	Suprapubic prostatectomy	1	Dead; cor. thrombosis
25	69	Cor. sclerosis; myocard. insuff.	6 mos.	38 24	154/70	170/70	160/70	33	Cystotomy	28	Improved

* T.P. = Transurethral prostatectomy. P.P. = Perineal prostatectomy. S.P. = Suprapubic prostatectomy.

duration the change may be immediate. Usually, however, it is a gradual fall over a period of days varying with the condition of the individual patient. While the patient is going through this renal and cardiovascular readjustment, there may be varying degrees of somnolence, weakness, anorexia and even disorientation. The duration of this period is inversely proportional to the efficiency of the myocardium and the renal function. The extent of fall in blood pressure is at times alarming, particularly in patients having definite cardiac disease. However, with proper care the pressure will usually rise again as myocardial efficiency increases and circulatory equilibrium again becomes established. There were 10 patients having a systolic blood pressure of 130 mm. Hg or less who exhibited no change in tension throughout the hospital stay. In general we regard the elderly patient with a low blood pressure as having a poorer outlook than the individual who maintains a pressure which is more usual at his age. The former condition may be a sign of a weak myocardium, or may be due to faulty peripheral circulatory dynamics.

Digitalis was administered to 18 patients and 7 did not require it. In spite of a recent cardiac accident, if there is no evidence of myocardial insufficiency digitalis is not usually employed. However, if there is doubt as to its necessity, the safer procedure is to give the drug.

The renal function tests employed were measurement of the concentrating power of the kidneys, the non-protein nitrogen of the blood, the fluid intake and output, and the excretion of phenolsulphonephthalein and diodrast. Only one of these patients had a fixed low specific gravity of the urine. The non-protein nitrogen of the blood of 14 patients was within normal limits throughout the hospital stay; 11 patients had definite elevation of the non-protein nitrogen at admission and in 6 of these it had become normal at the time of discharge from the hospital. There were 5 patients who exhibited a continual rise of the non-protein nitrogen for several days after vesical drainage was established. Only one of the 25 patients had a phenolsulphonephthalein excretion which could be judged as being within normal limits. Three patients had no excretion of phenolsulphonephthalein that was detectable and 7 had an excretion of less than 35% in 2 hours. Only 7 patients showed a significant increase of excretion of phenolsulphonephthalein during the hospital stay as evidence of improved renal function, yet 21 patients were definitely improved as judged by the clinical condition and by various laboratory tests. This illustrates somewhat the limitation of the value of the phenolsulphonephthalein test as a basis for clinical judgment.

According to the classification that we have used for convenience in the foregoing discussion, these 25 patients are found to be distributed in the following manner: Group 1, 12 patients; Group 2, 4 patients; Group 3, 9 patients.

As to the urologic treatment of these 25 patients, 2 were treated entirely by urethral drainage; cystotomy only was performed for 3; transurethral prostatectomy was done 8 times; perineal prostatectomy 5; and suprapubic prostatectomy 7.

The period of preparation before operation extended from 2 days to 1 year. Two patients, one prepared for 2 days and the other for 3 days before transurethral resection of the prostate, both died within 48 hours after operation of coronary thrombosis. One patient, aged 79, who had perineal prostatectomy after 28 days of suprapubic drainage, died 5 days after operation of renal failure owing to chronic pyelonephritis and nephrosclerosis. The other death occurred 24 hours after suprapubic prostatectomy in a patient aged 76 years. The cause of death was coronary thrombosis. Preoperative preparation lasted 35 days, during which time the non-protein nitrogen of the blood fell from 80 mg. to 32 mg. per 100 cc., but the blood pressure remained at 185/120 mm. Hg. Thus it is seen that even though a long period of preparation be carried out, one cannot always forestall cardiac accidents. However, such careful preparation tends to prevent many of them.

A careful choice of anesthesia and anesthetist is of great importance when the patient having heart disease must undergo a surgical procedure. In general, one wishes in these patients to avoid particularly sudden and extreme changes in blood pressure. The choice of anesthetic is determined for the individual patient by the nature of the operation to be performed and by the emotional stability of the patient. For those who are not apprehensive, a low spinal anesthesia is most suitable for transurethral or perineal surgery. When suprapubic cystotomy is necessary, local anesthesia with 1% procaine without adrenalin is satisfactory after analgesia by morphine. It has also been our experience that such patients tolerate exceedingly well gas-oxygen induction and ether anesthesia. This form is to be preferred for the nervous patient and for those in whom any sudden change in blood pressure would be particularly dangerous, *e. g.*, after a recent coronary thrombosis.

When general anesthesia is used for a patient with heart disease, the time and amount of anesthesia may be greatly reduced by having the patient prepared and in the proper position to begin the operation before induction is started. A quick induction with vinyl ether followed by ethyl ether is satisfactory under these conditions.

In a review of the surgical risk of patients with heart disease Butler, Feeney and Levine² have given the surgeon reason to maintain an optimistic attitude toward the results of necessary operative intervention. Of 500 consecutive patients who had prostatectomy in this hospital, there were 62 who had a history and definite signs of heart disease. Sixty-six operations were performed upon this group and there were 3 "unexpected" deaths. It was concluded that with careful cardiac therapy before and after operation, heart

disease itself was rarely a contraindication to necessary, timely prostaticectomy.

Conclusions. 1. A careful history is most important in eliciting evidence of heart disease.

2. Studies of exercise tolerance and vital capacity are of value in estimating the operative risk of elderly patients.

3. The patient who has recently been able to lead an active life is a good operative risk in spite of the presence of heart disease.

4. Acute urinary retention precipitated by an acute cardiac crisis does not always require subsequent prostatectomy. By careful judicious management it is often possible to tide such patients over by conservative means until cardiac decompensation has cleared and normal micturition been resumed.

5. The patient who tends toward recurrent cardiac decompensation with associated urinary difficulties, has progressively more severe urinary retention with each successive cardiac breakdown.

6. Several weeks should elapse after a coronary accident before resorting to surgery. In general the prognosis is better for these patients who have more than 4 weeks preoperative preparation, but this period must be judged on the basis of the merits of the individual case.

7. It is now more often a choice of the proper time to operate and the kind of operation to be employed rather than a decision for or against surgery, because modern methods do not impose a burden on even the diseased heart sufficient to upset its physiologic function when adequate medical care is given.

8. After prostatectomy great improvement is manifested in the cardiovascular condition of the patient who has had urinary retention and heart disease.

9. The operative approach and anesthesia depend on the characteristics and abilities of the patient, surgeon and anesthetist. In our clinic, the transurethral and perineal approaches have been used in recent years almost entirely, except when there is a definite and special indication for the suprapubic operation. The anesthesia of choice has been low spinal or ether.

10. Though one cannot always anticipate cardiac accidents, much can be done to forestall such events. By means of careful study of the patients in this age group, it is at least possible to designate those who are most likely to develop a cardiac complication and to render to these patients especial attention regarding stabilization of the circulatory system.

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THE MECHANISM OF A FORM OF GLOMERULONEPHRITIS*

NEPHROTOXIC NEPHRITIS IN RABBITS

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NEPHROTOXIC nephritis has been produced in guinea pigs,^{8,11} dogs,^{3,11} rats,^{9,13,14} and rabbits^{1,2,4,5,6,10,15} by the injection of antirenal sera. The remarkable clinical, pathologic, and physiologic similarity of this experimental disease to human glomerulonephritis has resulted in extensive investigations. The acknowledged virtue of nephrotoxic nephritis as a medium for investigation has, however, in a measure been dulled by the apparent absence of an analogy between the mechanism of the experimental disease and its counterpart in the human. If one accepts the concept that the experimental nephritis is produced by the direct action of the antibody contained in the nephrotoxic serum upon antigen inherent in the kidney, the only possible analogy that has been drawn is that in both instances—human and animal—the mediating influence is an antigen-antibody reaction.

That the above mechanism is not the cause of nephrotoxic nephritis in rabbits was suggested in a previous report by the author.⁶ Nephrotoxic duck serum was prepared by repeated intraperitoneal injections of rabbit kidney tissue into ducks. The injection of this serum into rabbits was followed, after a latent period of from 5 to 8 days, by the onset of nephritis. It was then demonstrated that the onset of the nephritis occurred shortly after the time of appearance of antibodies to duck serum in the circulating blood of the rabbit. In rabbits injected with duck serum, either normal or nephrotoxic, several days or weeks prior to the injection of nephrotoxic serum (the latter injection being preceded by desensitization to avoid anaphylaxis), antibodies to duck serum reappeared rapidly, and the duration of the latent period was shortened. In rabbits exposed to Roentgen rays in adequate dosage, antibodies to duck serum were not formed following the injection of nephrotoxic serum, and nephritis failed to appear. These findings suggested the hypothesis illustrated in Figure 1, a concept strongly supported by the experiments to be described, and one which lends itself to analogy with current concepts of the probable mechanism by which human glomerulonephritis develops.

This concept explains the latent period as the time required for the development of antibodies to duck serum, the shortening of the latent period in previously injected animals on the basis that the formation of antibodies is accelerated, and the failure to develop

* These studies were supported by the George deB. Keim Memorial Fund.

nephritis in rabbits exposed to Roentgen ray on the basis that the formation of antibodies to duck serum is completely inhibited. Although the results of the previous experiments appeared quite definite, it was felt that confirmation of the suggested hypothesis demanded further study, especially with regard to the mechanism by which the exposure of the rabbits to Roentgen ray so profoundly influenced the subsequent effects of the injection of the nephrotoxic serum.

**MECHANISM OF EXPERIMENTAL NEPHRITIS
PRODUCED IN RABBITS WITH NEPHROTOXIC DUCK SERUM**

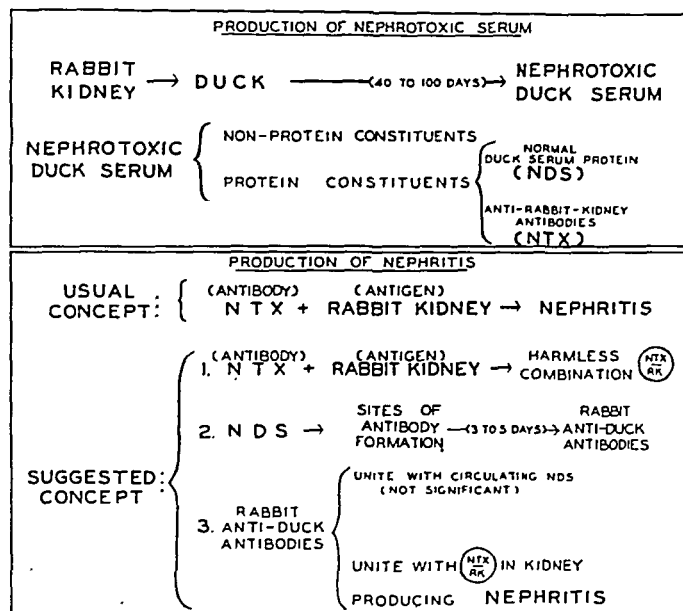


FIG. 1.—Mechanism of experimental nephritis, produced in rabbits with nephrotoxic duck serum.

Methods. The same strain of rabbits (mixed Dutch and American Blue) was used as in previous experiments. All weighed between 1700 and 2100 gm. Nephrotoxic serum was prepared by the repeated intraperitoneal injection of Pekin ducks with an emulsion of rabbit kidney. Roentgen ray was administered by a single 40 minute exposure of each entire animal with a total of 480 r.* Anti-duck-serum rabbit serum was obtained from rabbits which had received repeated intracutaneous injections of 0.5 cc. of normal duck serum at 6-day intervals. The formation of antibodies to duck serum and the disappearance of the injected duck serum from the circulation were studied by the precipitative methods previously described.

Results. Nine rabbits were injected with various doses of three different lots of nephrotoxin (NTX). During the 2-day period preceding the injection of the nephrotoxin, designated the desensi-

* Rabbits were treated with Roentgen ray under the direction of Dr. George P. Keefer, Fellow in Radiology, in this hospital.

tization period, all rabbits in these experiments received multiple increasing small doses of normal duck serum. This was done to make the results of these experiments strictly comparable with those of the preceding study where the desensitization procedure was necessary to avoid anaphylactic shock in rabbits reinjected with either normal or nephrotoxic duck serum.

The period of incubation before the development of the nephritis, as in previous observations, ranged from 5 to 8 days. There appeared to be no correlation between the size of the dose and the duration of the incubation period. In animals injected with large doses of NTX lot "B" or NTX lot "AB", abundant albuminuria with a few casts and minimal hematuria appeared immediately after the injection. This "false nephritis" completely disappeared within 48 hours. The urine then remained clear until several days later at the time of the true onset of the nephritis. The results of precipitative studies for the development of antibody to duck serum are shown in Figure 2.

Three rabbits were then exposed to Roentgen ray and injected with comparable doses of nephrotoxic serum. As previously observed in 8 other rabbits, nephritis did not develop, and as shown in Figure 2, no antibodies were formed.

A third group of rabbits were exposed to Roentgen ray, injected with nephrotoxic serum, and then injected with pooled anti-duck serum rabbit serum (ADS). Red blood cells obtained from each rabbit to be injected were tested for agglutination against the serum to be injected. No agglutination was observed. The ADS was administered to each rabbit as follows: 0.1, 0.2, 0.5, 1, 2, 5 cc., respectively at hourly intervals. The following day an initial dose of 2 cc. was followed by 6 cc., then two injections of 10 cc. each. The next day the serum was given in 3 doses of 10 cc. each. In rabbits XA-1 and XA-2 a somewhat different procedure was followed, but the principle of gradually increasing doses was likewise employed. In no instance was there any evidence of anaphylaxis. In the case of rabbits XA-1 and XA-2, the administration of the ADS was started on the day following the injection of the NTX. Nephritis did not develop in these rabbits. The other 4 rabbits of this group were identically injected with ADS on the fifth, sixth and seventh day. In each instance abundant albuminuria with casts and minimal hematuria appeared on the eighth day and persisted until the animal was sacrificed 9 to 12 days later. Grossly the kidneys were swollen and pale, with many punctate hemorrhages over the cortex. The microscopic pathologic changes were indistinguishable from those observed in normal rabbits injected with nephrotoxic serum, though less severe. As shown in Figure 2, changes in the circulating duck serum and antibody were quite similar to those which spontaneously developed in the normal rabbits.

Two rabbits (XR-1 and XR-2) were treated in exactly the same manner as XA-3, 4, 5, and 6, except that normal rabbit serum (NRS) was used instead of the ADS. Nephritis did not develop and precipitation curves were essentially as in the group exposed to

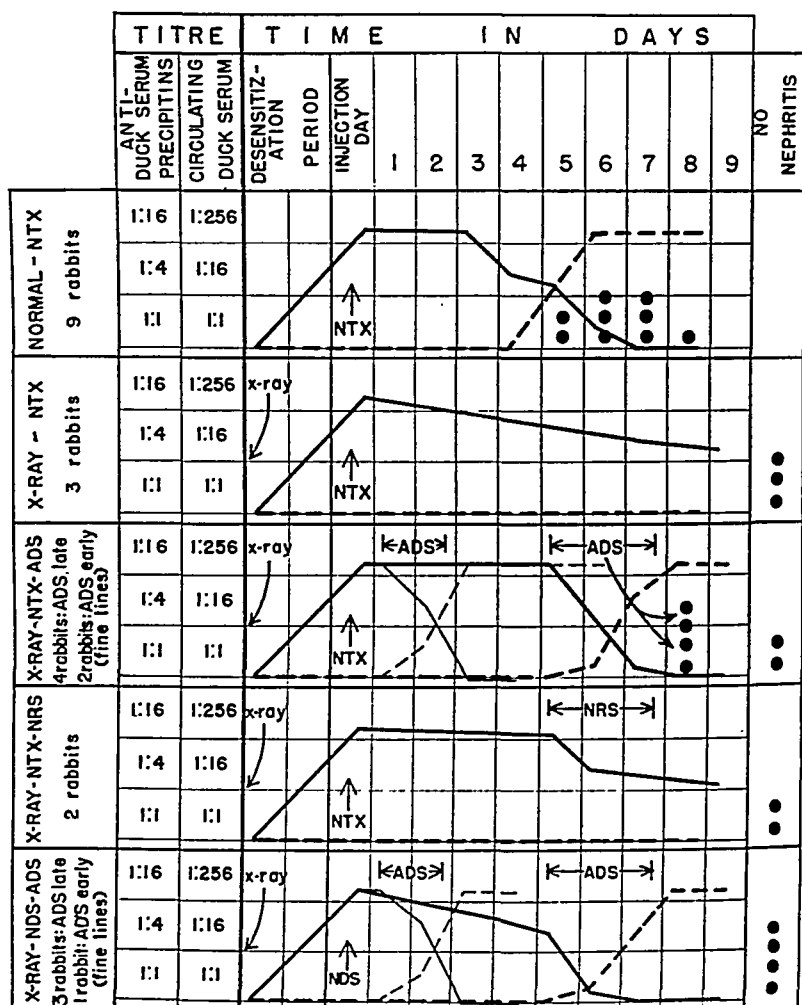


FIG. 2.—Disappearance of circulating duck serum (solid lines), development of precipitins to duck serum (broken lines), and clinical onset of nephritis (each dot represents 1 rabbit).

Roentgen ray and injected with NTX. A "false nephritis" was observed in these rabbits, but was not followed by the onset of the true nephritis.

A fifth group of 4 rabbits was tested in the same manner as the XA series except that normal duck serum (NDS) was given in place

of the NTX. Although the precipitation curves resembled those of the XA series, nephritis did not develop.

TABLE 1.—INFLUENCE OF NEPHROTOXIC DUCK SERUM, ROENTGEN RAY ANTI-DUCK-SERUM RABBIT SERUM, NORMAL RABBIT SERUM, AND NORMAL DUCK SERUM, ADMINISTERED IN VARIOUS COMBINATIONS, UPON THE DEVELOPMENT OF NEPHRITIS.

(Asterisk indicates rabbits in which a "false nephritis" appeared (see text).)

Series	Rabbit No.	Roentgen ray	Duck serum	Rabbit serum			Nephritis	
				Day	Cc.	ADS or NRS	Ap- pears	Day
I NTX	N-1	no	5.0 NTX "P"	..	no	..	yes	8
	N-2	no	5.0 NTX "P"	..	no	..	yes	6
	N-3	no	2.2 NTX "P"	..	no	..	yes	5
	N-4	no	6.0 NTX "P"	..	no	..	yes	5
	N-5	no	3.0 NTX "A"	..	no	..	yes	6
	N-6	no	6.0 NTX "A"	..	no	..	yes	6
	N-7	no	3.0 NTX "B"	..	no	..	yes	7
	N-8	no	6.0 NTX "B"	..	no	..	yes	7*
	N-9	no	5.5 NTX "AB"	..	no	..	yes	7*
II Roentgen ray: NTX	X-1	yes	6.0 NTX "P"	..	no	..	no	
	X-2	yes	6.0 NTX "P"	..	no	..	no	
	X-3	yes	6.0 NTX "A"	..	no	..	no	
III Roentgen ray: NTX: ADS	XA-1	yes	6.0 NTX "P"	1	20	ADS	no	
				2	40	ADS		
	XA-2	yes	6.0 NTX "P"	1	25	ADS	no	
				2	60	ADS		
	XA-3	yes	6.0 NTX "A"	5	8.8	ADS	yes	8
				6	28	ADS		
				7	30	ADS		
	XA-4	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
				7	30	ADS		
	XA-5	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
				7	30	ADS		
	XA-6	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
IV Roentgen ray: NTX : NRS	XR-1	yes	5.5 NTX "AB"	5	8.8	NRS	no	*
				6	28	NRS		
				7	30	NRS		
	XR-2	yes	5.5 NTX "AB"	5	8.8	NRS	no	*
				6	28	NRS		
				7	30	NRS		
V Roentgen ray: NDS : ADS	XNA-1	yes	5.5 NDS	1	20	ADS	no	
				2	40	ADS		
	XNA-2	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		
	XNA-3	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		
	XNA-4	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		

For additional rabbits in Series 1 and 2, similarly treated and studied, with identical results, see Reference 6. The author had intended to include additional animals in each of the three lower groups. This was prevented by the accidental destruction of some of the necessary sera. Conclusions, however, seem valid in view of the complete uniformity of results in rabbits similarly treated.

A summary of these experiments is shown in Table 1. It is seen that nephritis developed in rabbits exposed to Roentgen ray, injected with nephrotoxic serum, an interval allowed to elapse, and then injected with anti-duck serum. Nephritis did not develop when normal rabbit serum was substituted for anti-duck-serum rabbit serum or when normal duck serum was substituted for nephrotoxic serum.

Discussion. These experiments appear to complement those previously reported in establishing the mechanism illustrated in Figure 1 as that which is operative in the production of nephrotoxic nephritis in rabbits. Antibodies were passively transferred to attack an antigen combined in the kidney, whereas in the normal rabbit injected with nephrotoxic serum, the antibodies are formed by the rabbit, attacking the antigen combined in the kidney. In view of the demonstration⁶ that the nephrotoxic component can be removed by the simple perfusion of the nephrotoxic serum through a rabbit kidney, it is of interest to note that the nephritis does not develop when the anti-duck serum injections are started 24 hours after the injection of the nephrotoxin. This would appear to indicate that the nephrotoxic component, though bound to the kidney, had not yet become incorporated into or combined with the kidney cells, and hence was destroyed by the anti-duck antibodies without renal damage. Analogy may be made with the many observations that a time interval is required between the injection of antigen and the injection of antibody for successful passive transfer anaphylaxis.

The failure of nephritis to develop in rabbits exposed to Roentgen ray, injected with nephrotoxic serum, and then with normal rabbit serum appears to eliminate the possibility that Roentgen ray may destroy complement and thus prevent an antigen-antibody reaction. From the fact that nephritis was not induced by the passive transfer of anti-duck antibodies in rabbits injected with normal duck serum it is apparent that a non-specific reverse anaphylaxis was not an essential factor.

With the exception of the guinea pig, in which the response to the injection of nephrotoxic serum is complicated by hemolytic and anaphylactic phenomena,^{8,11} the one striking variation in the nephritic response of the different species of animals in which nephrotoxic nephritis has been studied is in the duration of the latent period between the time of injection and the time of onset of the nephritis. A latent period of at least 5 days has been uniformly observed in rabbits injected with nephrotoxic duct serum. A latent period of 6 to 10 days was noted by Fouts, Corcoran, and Page³ in dogs injected with nephrotoxic serum prepared in the hen. The mechanism demonstrated here as the cause of nephritis in rabbits would appear applicable by analogy to these dogs. The concept cannot, however, be applied without modification to nephritis produced in rats by the injection of nephrotoxic rabbit serum,^{9,13,14} or to the nephritis produced in dogs by the injection of nephrotoxic rabbit serum,¹¹ for

in these instances renal changes appear within a few hours after the injection of the serum. In our experiments occasional lots of nephrotoxic serum were found to produce a "false nephritis" within a few hours after the injection—massive albuminuria with casts and a very few red blood cells. These urinary abnormalities completely disappeared, to reappear several days later with the onset of the true nephritis, unless the mechanism responsible for the latter were suppressed by the use of Roentgen ray. This phenomenon was likewise observed by Fouts, Corcoran, and Page³ in dogs. Consideration must be given to the possibility that the apparent absence of the latent period in rats and in Pearce's dogs was due to an imperceptible blending of a "false nephritis" into the true nephritis. If so, urinary abnormalities should rapidly disappear in animals exposed to doses of Roentgen ray adequate to inhibit antibody formation. It may or may not be mere coincidence that nephrotoxic sera derived from rabbits produce an immediate response (in guinea

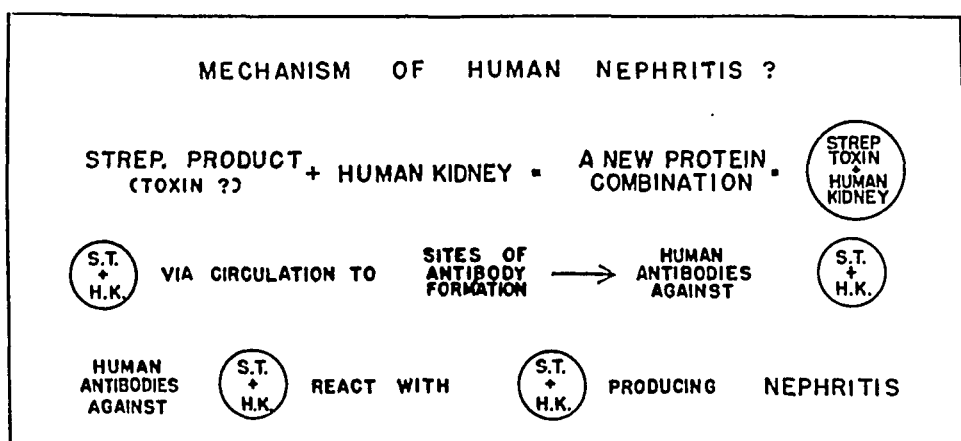


FIG. 3.—Suggested concept of the mechanism of human glomerulonephritis (see text).

pigs, rats, and dogs), whereas sera derived from fowl (duck, hen) are associated with a latent period (in rabbit and dog).

An interesting concept of an antigen-antibody mechanism as the cause of acute glomerulonephritis in man has been recently introduced by Schwentker and Comploier.¹² They suggested that renal cell proteins are altered by some product of the streptococcal infection, and that this altered renal protein constitutes a new antigen, introduced into the circulation as the damaged renal cells are repaired. As a result, antibodies are produced which react with the altered renal proteins, and possibly also with normal renal proteins through an immunologic relationship to which the term *haptens* is applied, to produce nephritis (Fig. 3).

This concept offers a more nearly satisfactory interpretation of the clinical characteristics peculiar to human glomerulonephritis than any concept suggested heretofore; and it is not at variance with known facts in any basic particular. It offers an explanation for

the rôle of streptococci, for the latent period between the infection and the onset of the nephritis, for the shortening of the latent period in exacerbations of the disease, and for the absence of bacteria in the nephritic kidneys. It is, however, based more upon circumstantial evidence and analogy than upon factual support. Kay, Lucchesi, and Rutherford⁷ were unable to demonstrate antibodies to human kidney antigens in the sera of a large group of patients with scarlet fever. The negative results obtained, while failing to give support to the concept, could by no means be considered a conclusive test of the validity of the concept for reasons discussed in their presentation. The mechanism of nephrotoxic nephritis, here described, may be considered to offer some further support, by analogy, for the concept of Schwentker and Comploier.¹² In the rabbit, antigen is bound to or combined with the kidney cells because of an immunologic affinity. In man, the antigen is formed in the kidney by the action of some product of the streptococcal infection upon the kidney cells. In both animal and man, a latent period ensues for the development of antibodies, and in both, nephritis develops as the result of the reaction of these antibodies with antigen combined with or bound to the kidney cell proteins.

Summary. 1. Nephritis was produced in rabbits by the injection of nephrotoxic duck serum.

2. Nephritis did not develop in rabbits exposed to Roentgen ray before the injection of the nephrotoxic serum.

3. Rabbits exposed to Roentgen ray and injected with nephrotoxic serum were made to develop nephritis by the passive transfer of antibodies to duck serum.

4. These results appear to justify the conclusion that the mechanism of nephrotoxic nephritis in rabbits previously suggested by the author is correct (see Fig. 1). Analogy is drawn between this mechanism and recent concepts of the mechanism by which human glomerulonephritis develops.

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NON-DIABETIC GLYCOSURIA

A FOLLOW-UP STUDY WITH GLUCOSE TOLERANCE TESTS

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It is the purpose of this paper to present the results of our studies upon selected cases with glycosuria in order to determine the prognostic significance of apparently non-diabetic glycosuria.

It has been repeatedly stated that non-diabetic glycosuria is without serious consequences. Marble, Joslin, Dublin and Marks⁸ state that "Non-diabetic glycosuria in itself has little or no adverse influence upon longevity." These authors point out the paramount importance of adequate initial study to establish the true nature of the glycosuria. John⁴ is of the opinion that "There is sufficient evidence in the literature to support the statement that non-diabetic glycosuria remains so throughout the years. . . . and is not a transitory state toward diabetes." Lawrence⁷ writes as follows: "If normoglycemic glycosuria is proved by a thorough investigation, such as the finding of a normal glucose tolerance test, then I think the whole condition can be neglected at once and forever." In general, our studies tend to substantiate these statements.

Methods. Subjects were chosen from a group of individuals who had submitted to glucose tolerance tests 5 to 13 years ago because of a previous finding of glycosuria in the course of an examination for life insurance. Most of the subjects selected for follow-up had clearly normoglycemic curves with glycosuria, but a few borderline glucose tolerance curves are included for comparison. One hundred and nine individuals were invited to participate but only 32 accepted. Five additional cases could be followed up from existing records. The majority of cases were restudied with the conventional 1-dose, 2-hour test employing 1 dose of 50 gm. of glucose. A few cases recorded in the latter portion of Table 1 were studied by the Exton-Rose, two-dose technique¹ in both the original study and the follow-up or they may have received the 1-dose test in 1 instance and the 2-dose in another.

Interpretation of Blood Sugar Values. Capillary blood sugar values are reported throughout Table 1 because these were used in all the original studies. Capillary blood sugar values may be unpredictably higher than simultaneously determined venous blood sugar values especially during the peak of the curve at $\frac{1}{2}$ or 1 hour. This is true both in the conventional 1-dose technique or in the 2-dose Exton-Rose technique. Two hours after the ingestion of glucose the capillary and venous blood sugar values are often nearly the

TABLE 1.—FOLLOW-UP STUDY OF NON-DIABETIC GLYCOSURIA

(One-dose, 2-hour glucose tolerance test used except in those cases marked with an asterisk, which indicates a 1-hour value of the 2-dose, 1-hour technique, Exton-Roso)

Original study			Follow-up study							
Subject	Blood sugar tolerance, mg. per 100 cc.			Glycosurin, %	Blood sugar tolerance, mg. per 100 cc.			Glycosurin, %		
	Date	Fasting	2-hour		Date	Fasting	2-hour			
1 E. P. W.	7-13-31	113	190	125	0.5	2-19-37	105	200	66	+
2 L. R.	8-15-34	65	130	80	3.0	8-25-39	120	140	95	1.0
3 G. M.	3-10-34	106	171	88	+	3-17-40	85	175	92	0.4
4 R. S. M.	3-9-37	88	157	80	3.0	12-30-40	76	..	93	2.0
5 J. P.	2-26-29	110	206	70	+	4-28-41	110	190	95	0.5
6 E. D. B.	12-10-29	114	180	96	0.5	6-2-41	100	190	123	1.0
7 J. W. W.	1-28-30	105	206	71	+	7-14-41	78	143	90	1.0
8 E. L. S.	9-25-30	100	196	127	+	5-19-41	75	112	130	0.5
9 G. S. M.	7-14-31	109	171	147	0.4	6-3-41	90	133	83	0.3
10 W. H. B.	1-26-32	99	178	118	1.0	5-13-41	110	168	185	10.0
11 J. H. M.	4-7-32	91	167	121	0.2	6-25-41	82	162	110	0.5
12 H. S.	7-5-32	92	155	96	0.5	6-11-41	80	120	70	0.2
13 J. P. G.	10-19-32	110	188	145	1.0	5-27-41	110	198	105	1.5
14 W. B.	2-9-33	97	123	133	0.4	0-25-41	90	115	83	0.0
15 D. H. W.	3-31-33	95	121	101	1.0	6-18-41	90	132	97	0.5
16 O. W.	8-8-33	93	161	86	0.5	5-10-41	75	102	60	0.3
17 J. M.	9-22-33	91	182	108	1.0	0-18-41	92	103	73	0.0
18 M. M.	11-17-33	98	167	146	0.2	6-26-41	120	230	185	3.0
19 M. S.	3-27-33	..	153	74	0.4	5-27-41	88	138	94	0.5
20 H. W. M.	12-13-33	112	270	132	1.0	7-6-41	85	183	93	0.2
21 A. R.	7-31-34	109	155	88	0.4	5-15-41	88	134	82	0.5
22 E. H. E.	12-2-35	80	174	100	0.5	6-22-41	96	135	92	0.5
23 F. H. O.	12-9-33	110	161	95	1.0	8-16-41	90	136	97	3.0
24 G. H. H.	5-31-33	80	180	99	1.0	8-16-41	95	176	105	5.0
25 S. C. H.	6-20-31	114	168	137	0.3	8-14-41	83	115	121	0.0
26 J. M.	12-11-34	80	125	85	1.0	1-17-42	75	140	70	4.0
27 T. J. B.	6-29-30	90	204	95	+	1-6-42	95	145	80	0.0
28 A. H.	2-27-37	80	138	80	+	2-25-42	100	145	80	0.5
29 D. F. B.	9-21-29	80	145	80	3.0	Known glycosuria since 1924.				Recent fasting blood sugar,
30 R. O.	6-25-36	83	208	83	2.0	84 mg.				
31 J. V. L.	3-3-37	92	148	160*	0.3	7-29-41	100	195	155*	0.5
32 F. C. B.	8-3-36	80	150	180*	4.0	8-5-41	78	130	135*	0.3
33 W. H. D.	6-18-36	88	142	152*	1.5	3-19-41	85	199	173*	0.5
34 E. S.	12-26-34	90	150	140*	0.5	8-12-41	90	140	154*	0.4
35 L. C. S.	12-15-34	100	210	105	0.3	8-1-41	95	203	273*	3.0
36 L. D.	12-17-35	97	157	110	0.5	5-8-41	94	150	140*	0.5
37 H. J. R.	5-22-36	100	160	180*	1.0	7-30-41	80	180	60	0.5
		95	150	155*	1.0	8-11-41	97	195	200	5.0

same although the capillary blood sugar may be 10 or even 20 mg. per 100 cc. higher than the venous blood sugar. At any rate, one may be sure that the capillary blood sugar will always be higher than the venous blood sugar except in severe diabetes with which we are not dealing here. In this study, venous and capillary blood sugar values were determined simultaneously in many of the follow-up studies; and in each of the 4 individuals (Cases 10, 18, 34 and 37) to be discussed later, who ultimately developed abnormal glucose tolerance responses, the diagnosis was substantiated by the venous blood sugar values.

Criteria. Based upon our previous experience with a comparison of capillary and venous blood sugar values⁵ and a consideration of criteria for interpretation of the two types of glucose tolerance techniques which we reviewed in a previous paper,⁶ we offer the following criteria for the interpretation of the 1-dose, 2-hour test using capillary blood: For a clearly normal response, a fasting blood sugar of 120 mg. per 100 cc. or less, a $\frac{1}{2}$ -hour value of 200 mg. per 100 cc. or less, and a 2-hour value of 120 mg. per 100 cc. or less. These criteria for capillary blood may appear to be rather severe when one considers the fact that capillary blood sugar values may be much higher than venous blood sugar during the postabsorptive period. However, this difference is so variable and unpredictable that the only safe procedure is to consider a blood sugar tolerance curve which exceeds the above-mentioned criteria as being potentially abnormal.

Criteria for the 2-dose test using capillary blood are even more difficult to define but we have selected 180 mg. per 100 cc. or less for the hour value as a normal response for capillary blood providing the fasting sugar is also normal, the amount of rise or fall during the second half hour is not taken into consideration.

Results. Of the 37 cases that were restudied after a period of 5 to 13 years, 4 developed abnormal glucose tolerance curves. In 1 of these (Case 18) the original study had resulted in a borderline blood sugar curve although a 2-hour value of 146 mg. per 100 cc. of capillary blood may be seen in a non-diabetic individual. In the other 3 (Cases 10, 34 and 37) the blood sugar figures were definitely within normal limits at the time of the original examination although 1 (Case 10) had a 2-hour value at the upper limit of normal and another (Case 34) had a $\frac{1}{2}$ -hour value that was somewhat high. On the other hand, many of the individuals who did not develop diabetes had original blood sugar curves as high or higher than those individuals whose blood sugar tolerance curves were abnormal on follow-up study.

The percentage of sugar excreted in the urine seemed to be of no prognostic value, indeed, curiously enough, in the individuals we studied those who excreted the most sugar did not develop diabetes (see Table 1).

Discussion. As early as 1922 Holst³ found the causes of non-diabetic glycosuria to be an abnormally low renal threshold, high alimentary rise, or a combination of the two. Marble and Joslin's⁸ definition of true renal glycosuria requires the presence of glucose in fasting as well as postprandial urine, an unusual condition. The great majority of non-diabetic glycosurias have a threshold that is exceeded only after the ingestion of a moderate amount of carbohydrates. None of our subjects would qualify as renal glycosuria according to Joslin's definition. With regard to intermittent and continuous glycosuria Fischer² feels that it seems unnecessary to separate arbitrarily the two types of renal glycosuria for they are benign, frequently familial and are differentiated only by the height of the renal threshold for glucose. Regardless of one's classification of non-diabetic glycosuria it is the consensus of opinion that the condition is benign. John⁴ in a summary of the literature has shown that individuals may put out large quantities of sugar for years without detriment to themselves. Our results are in agreement with this finding (Table 1). Thus it is evident that the excretion of a large amount of sugar is not necessarily associated with an unfavorable prognosis. When one obtains an unequivocally normal blood sugar tolerance curve especially on more than one occasion it seems unimportant whether the individual has little or much glycosuria. The amount of glycosuria with normal postabsorptive blood sugar levels is purely and simply a function of the renal threshold for glucose. In discussing non-diabetic glycosuria, Marble, Joslin, Dublin and Marks⁸ state: "Caution must be advised against accepting as normal, tolerance curves which either at the highest point or subsequent fall are on the borderline of the type found in mild diabetes." We believe that the importance of this cannot be overemphasized and in our experience this statement is equally true whether there is glycosuria or the urine is sugar-free. Any borderline glucose tolerance curve should be rechecked by a repetition of the test after all the factors which may have influenced it have been considered and corrected.

Of the 109 cases of glycosuria with normal or borderline glucose tolerance tests which we attempted to follow-up, 8 could not be contacted because of incorrect addresses, 19 did not reply to two or more letters, 35 either declined to have the study done or accepted but failed to keep their appointment for the test, of these at least 3 are known to have developed diabetes, 10 of the individuals had died, but in none of these was diabetes mentioned as a contributing cause of death, and 37 yielded the information which is summarized in Table 1. All the individuals in the group studied were symptom-free and considered themselves in good health, even those with apparent diabetes.

An interesting question presents itself. Why did 3 individuals with normal blood sugar curves out of a group of 36 cases of glyco-

suria develop probable diabetes? This is much higher than the average chance of developing diabetes. Several possibilities suggest themselves: 1, Obviously a technical error in the original study may have occurred in the determination of the blood sugar curve. 2, The reason for performing the original study was the previous finding of glycosuria; this may have been due to a diminished ability to metabolize glucose. Repeated glucose tolerance curves upon the same individual will show considerable variation. The original glucose tolerance curves in our study may have been performed at a time when a coincidence of favorable circumstances produced a tolerance curve within top normal limits in a very mild diabetic with a lower than average renal threshold for glucose. This possibility emphasizes the need for more than one tolerance study in the evaluation of this type of case. 3, High peak values which some observers consider to be of prognostic significance may have been missed by taking specimens at only $\frac{1}{2}$ and 2 hours. 4, Our study tends to disprove the possibility that the diabetic organism has more tendency to excrete glucose than a normal individual at a given blood sugar level. In fact, this possibility seems very unlikely since both mild diabetics with only moderately elevated blood sugar levels and severe diabetics with high blood sugar levels may fail to excrete glucose due to a high renal threshold for glucose.

Whatever the reason, it seems to be a fact that when conclusions are drawn from a single glucose tolerance test, an individual with apparently non-diabetic glycosuria is more likely to develop diabetes than a normal individual. This has also been the experience of Marble *et al.*⁸

Summary. 1. In a group of 37 individuals with apparently non-diabetic glycosuria, based upon one glucose tolerance curve obtained 5 to 13 years ago a greater number developed diabetes than can be accounted for on the basis of chance.

2. The amount of glucose in the urine was, in itself, of no prognostic significance.

3. If glycosuria is proven by thorough study and continued observation to be truly non-diabetic, it appears to be without detriment to health.

We wish to acknowledge the technical assistance of Harry L. Fies.

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A QUANTITATIVE STUDY OF THE VARIATIONS IN MULTIPLE STERNAL MARROW SAMPLES TAKEN SIMULTANEOUSLY

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THE early investigators^{1,4,7} of sternal puncture regarded the procedure as a qualitative one. Bone marrow smears were examined for cellular content just as the pathologist examines any other aspirated fluid. During the years that followed, sternal puncture became increasingly popular, and a large literature on the subject arose. Many modifications of technique were suggested, as is usually the case with a new procedure. Quantitative determinations^{2,3,9,10,11} of the different marrow constituents were emphasized with increasing frequency, until the marrow is now studied with the same care and precision as the peripheral blood. Certain workers⁶ have gone so far as to develop fixed ratios between the various types of marrow cells, and to attempt to draw conclusions from variations in these ratios. These studies would correspond to the Arneth and Schilling indices for the peripheral blood. Unfortunately, the material aspirated by sternal puncture is not like the blood, and cannot be studied with the same degree of accuracy. The peripheral blood is homogeneous throughout the body, and it is to be expected that a quantitative determination made from any accessible region would be accurate. That this is the case is shown by the fact that multiple samples taken simultaneously from different places check very closely when studied quantitatively.

In marrow studies we find certain inherent fundamental discrepancies which make accurate quantitative determinations impossible. The interior of the sternum is composed of spongy bone, in the interstices of which, the marrow cells are held as a loose tissue. The peripheral blood circulates freely throughout the interior of the sternum in channels called sinuses. The cellular structure of the marrow is not uniform, since it is composed of different groups of cells, namely, granulocytes, erythroid cells and megakaryocytes. These cells are arranged in clusters of a similar type. When a needle is forced into the marrow cavity, admission is made possible by the penetration of the cortical bone and breaking down of some bone spicules. The puncture site is open to variation, as is also the depth to which the needle is inserted. The degree of suction employed cannot, of necessity, always be the same, and the amount of peripheral blood aspirated is very often dependent on conditions within the sternum. The existence of these factors makes it obvious that the aspirated material could

not be homogeneous like the peripheral blood. It seems permissible to make qualitative studies on this material just as with tissue, and, to some degree, rough quantitative determinations as previously pointed out.⁸ In order to substantiate this contention, the following experiment was devised and carried out.

Method. A series of 26 patients was selected for study. From each of these 4 samples of marrow were taken. This was accomplished as follows: 2 sternal punctures were done at the same time on each patient, 1 immediately following the other. One puncture was made in the second interspace, the other in the third. From each puncture 2 separate marrow samples were aspirated and labeled Ia, Ib, IIa and IIb. Each sample consisted of 2.5 cc. of fluid which was placed in a tube containing 0.5 cc. of 1.4% sodium oxalate solution evaporated to dryness, to prevent coagulation. Direct smears on slides were also made from each sample at this time. Total nucleated cell counts were done on each sample, and the slides were stained with Jenner-Giemsa stain, after which differential counts of 500 cells were done. The counts were all done by one of us (C. R.). A total white count of the peripheral blood was also done in each case. These data were then tabulated and subjected to statistical analysis.* The tables follow (pp. 498-501).

Discussion. Table 2 shows for several groups of diseases the mean and standard deviation for the total nucleated white cell count and number of polys. Except for diseases of the blood-forming organs, the number of observations in each group was small, and the average of the samples obviously has little meaning except for a study of the variability. The highest mean and standard deviation for the total white count was observed among diseases of the nervous system which included 2 cases with relatively high counts, and 1 case with low counts. The highest and most variable average number of polys was observed in the largest group, *i. e.*, among diseases of the blood-forming organs.

Since an inspection of the individual counts seemed to indicate that there was often as great a variation between cases of the same group, the statistical comparisons were made of the standard deviations from the mean of the 2 samples and 4 samples from the same case. Table 3 shows the standard deviation from the mean white cell count for the two counts from the same sample (pairs) compared with the standard deviation from the mean of four counts from 2 samples taken simultaneously (quartettes). For diseases of the blood-forming organs the standard deviations for the pairs of counts is 9583 ± 611 cells and for the four counts $11,619 \pm 740$ cells with a difference only twice its probable error or 2035 ± 960 . The standard deviation from the mean of all the counts from the same group as shown in Table 3 was $25,426 \pm 1620$ cells which differed from the standard deviation from the mean of four counts from the same case by $13,807 \pm 1782$ cells or a difference which is nearly

* The authors wish to thank Dr. W. F. Dunning and Dr. M. R. Curtis of the Crocker Institute, Columbia University, for their help in analyzing the data and interpreting the results.

TABLE 1.—ABSOLUTE NUMBERS FOR MULTIPLE SAMPLES OF STERNAL MARROW

Case No.	Age	Sex	Diagnosis	Red cell count (millions per c.mm.)	White count of peripheral blood (thousands per c.mm.)	Marrow sample	Total nucleated cell count (thousands per c.mm.)	Neutrophil, mature	Neutrophil bands	Metamyelocytes	Neutrophil myelocytes and premyelocytes	Eosinophilic myelocytes	Myeloblasts	Eosinophils	Monocytes	Lymphocytes	Lymphoblasts	Basophils	Plasma cells	Proerythroblasts	Erythroblasts	Normoblasts	Megakloblasts	
1	36	M	Chronic arthritis	3.8	13.2	Ia	37.0	12,506	8,214	1,258	3,996	370	222	962	222	1,998	0	0	0	0	4,884	2,368	0	
						Ib	45.0	12,900	12,600	720	6,390	360	540	1,800	360	1,980	0	180	0	0	4,590	2,340	0	
						IIfa	104.0	29,536	18,928	2,912	23,083	1,664	208	4,368	416	208	0	0	0	15,600	7,072	0		
2	32	F	Pernicious anemia	3.9	9.8	IIfb	60.0	15,600	15,840	2,400	9,600	600	600	1,920	240	3,600	0	240	0	0	4,200	5,040	0	
						Ia	35.6	16,447	4,130	854	2,990	0	0	356	0	3,062	0	0	0	0	3,774	3,987	0	
						Ib	42.0	18,228	5,460	924	5,292	0	84	336	81	1,761	0	0	0	0	4,872	4,956	0	
3	57	F	Secondary anemia	3.5	7.8	IIfa	57.4	17,079	13,432	2,066	8,840	115	1,492	115	0	4,607	0	230	0	0	4,133	4,592	0	
						IIfb	38.0	15,200	9,424	1,824	3,192	0	380	304	0	2,508	0	0	0	0	1,140	4,028	0	
						Ia	39.4	15,524	5,122	1,655	3,782	315	79	315	630	2,049	0	0	0	0	6,383	3,310	0	
4	41	F	Gangrene of fingers	4.2	12.0	Ib	19.2	8,563	2,381	192	2,266	38	0	115	0	499	0	0	0	77	2,573	2,496	0	
						IIfa	22.0	3,080	3,916	352	6,248	396	0	220	0	1,408	0	44	0	0	2,244	3,740	0	
						IIfb	20.6	6,221	3,090	1,071	5,315	288	0	618	0	1,277	0	0	0	0	1,112	1,442	0	
5	47	M	Cirrhosis of liver	5.3	10.8	Ia	118.0	29,028	29,028	8,260	17,228	1,652	1,416	2,124	0	3,776	0	0	236	944	1,156	12,744	0	
						Ib	81.0	21,384	23,976	7,938	8,910	486	486	2,592	162	3,888	0	0	162	0	5,022	5,994	0	
						IIfa	60.0	20,160	13,680	4,800	10,800	720	0	1,200	120	1,080	0	0	240	120	3,960	3,120	0	
5	47	M	Cirrhosis of liver	5.3	10.8	IIfb	133.0	28,196	26,008	7,980	25,536	3,458	532	5,054	266	532	0	0	0	0	266	17,290	17,822	0
						Ia	40.0	18,160	4,480	720	3,360	0	160	610	400	5,280	0	0	80	0	3,040	3,600	0	
						Ib	29.0	11,918	5,336	986	3,361	116	171	174	58	2,378	0	0	0	0	1,102	3,364	0	
5	47	M	Cirrhosis of liver	5.3	10.8	IIfa	42.0	14,616	7,476	1,680	6,636	0	756	252	420	4,368	0	81	0	0	1,311	4,032	0	
						IIfb	35.0	11,770	6,160	490	6,636	70	210	420	560	1,050	0	0	0	0	2,170	2,430	0	

6	45	F	Pernicious anemia	4.0	9.8	Ia Ib IIa IIb	23.4 22.2 53.2 45.2	7.722 8.924 21.706 13.922	4.332 3.508 8.299 9.402	1.198 488 2,979 3,254	2.855 2,886 6,597 7,684	328 178 745 362	140 133 213 362	374 222 1,915 814	281 622 638 0	983 2,012 2,660 2,441	0 0 0 0	0 44 0 0	0 47 0 0	231 0 319 90	2,574 2,042 3,016 3,616	2,012 1,066 1,170 3,254	0 0 0 0
7	51	F	Pernicious anemia	4.5	10.0	Ia Ib IIa IIb	12.0 15.4 12.2 15.0	7.296 7.392 8.150 8.520	1,752 3,142 1,049 2,100	96 493 0 300	1,248 2,464 1,659 1,920	0 123 24 60	108 185 24 60	72 62 73 240	336 400 488 690	432 246 317 390	0 0 0 0	0 0 0 0	0 31 24 0	336 616 268 540	264 246 122 180	0 0 0 0	
8	11	M	Congenital lues	4.5	6.4	Ia Ib IIa IIb	66.8 62.0 78.0 34.4	10.955 20.460 17.160 9.426	10,020 13,208 9,828 7,430	1,737 3,100 4,056 1,514	7,214 6,324 10,608 3,784	401 124 156 344	2004 620 624 413	134 496 780 550	0 372 156 0	14,295 4,836 4,836 3,509	0 0 0 0	134 124 0 0	134 372 1872 344	12,826 7,440 16,224 3,715	6,850 4,464 11,700 3,371	267 0 1,700 0	
9	11	M	Trichinosis	4.4	15.0	Ia Ib IIa IIb	88.0 41.8 77.0 106.0	15.312 7.022 13.552 14.204	9,328 6,103 12,628 10,292	4,400 1,087 2,772 3,604	10,384 3,511 15,092 16,536	11,616 2,174 8,932 6,360	880 418 616 2544	17,072 15,048 14,938 24,380	0 167 0 848	2,816 2,257 0 3,180	0 0 0 0	352 84 462 0	0 0 0 0	880 167 308 424	10,208 2,592 6,776 5,512	4,752 1,170 924 8,904	0 0 0 212
10	60	M	Hemiplegia	4.5	11.0	Ia Ib IIa IIb	57.4 128.0 86.0 72.0	24.567 47.104 30.444 22.832	11,480 36,698 20,984 17,856	2,066 3,584 4,816 2,016	6,544 19,200 11,524 7,776	230 1,536 688 288	0 0 172 144	574 2,304 860 1,584	0 0 0 0	4,592 2,816 7,396 4,608	0 0 0 0	0 0 0 0	230 512 516 144	4,822 7,168 2,752 1,728	1,952 7,168 5,848 3,024	0 0 0 0	
11	20	M	Lymphadenitis	4.4	5.6	Ia Ib IIa IIb	50.0 38.0 54.0 45.0	19.100 12.008 19.761 18.270	9,800 9,728 11,988 10,440	1,200 2,052 1,188 630	5,000 5,396 5,832 6,660	400 304 432 360	500 304 432 720	800 0 972 630	100 0 0 630	3,100 4,104 5,400 1,800	0 0 0 0	0 0 324 0	0 76 432 180	3,100 1,520 2,484 1,890	6,600 2,280 4,752 1,890	0 228 0 0	
12	41	F	Hepatosplenomegaly	4.2	10.0	Ia Ib IIa IIb	9.2 13.4 20.2 14.0	4.105 6.834 6.026 6.692	754 1,234 3,515 1,232	110 134 567 224	662 1,179 2,424 1,512	37 80 121 56	37 0 323 0	221 322 425 448	570 456 444 336	1,251 1,420 2,141 2,100	0 0 0 0	18 27 81 28	0 0 91 28	607 965 1,656 1,344	718 750 1,737 0	0 0 0 0	
13	61	F	Hodgkin's disease	4.7	55.0	Ia Ib IIa IIb	105.6 80.0 102.0 60.0	46.290 29.600 39.931 18.960	7,140 4,000 11,016 3,720	1,050 1,920 1,428 480	14,070 6,560 13,872 7,080	210 320 204 0	630 480 1836 480	3,780 4,480 3,468 840	1050 640 0 480	3,360 2,240 1,836 1,200	0 0 0 0	1470 0 204 240	0 160 0 0	11,760 6,400 6,936 6,480	14,280 23,200 21,216 20,040	0 0 0 0	

TABLE 1.—ABSOLUTE NUMBERS FOR MULTIPLE SAMPLES OF STERNAL MARROW—Continued

Case No.	Age	Sex	Diagnosis	Red cell count (millions per c.mm.)	White count of peripheral blood (thousands per c.mm.)	Marrow sample	Total nucleated cell count (thousands per c.mm.)	Neutrophil, mature	Neutrophil bands	Metamyelocytes	Neutrophil myelocytes and premyelocytes	Eosinophilic myelocytes	Myeloblasts	Eosinophils	Monocytes	Lymphocytes	Lymphoblasts	Basophils	Plasma cells	Proerythroblasts	Erythroblasts	Normoblasts	Megakaryoblasts
14	17	F	Trichinosis	4.1	19.5	Ia Ib IIa IIb	88.0 59.2 76.0 54.8	20,708 17,405 18,818 18,742	21,296 12,077 12,160 9,206	4,752 5,446 4,560 2,850	8,624 2,486 8,816 4,055	4,400 2,186 4,560 1,754	528 0 912 219	8,272 0 8,360 6,466	704 1302 1976 1315	6,512 4,026 2,432 5,151	0 0 0 0	528 0 0 110	1408 237 152 0	176 118 1216 219	5,280 2,368 8,816 2,959	4,752 4,262 3,192 1,754	0 0 0 0
15	40	M	Polycythemia vera	7.2	35.6	Ia Ib IIa IIb	102.1 132.4 51.4 67.4	42,598 65,070 29,709 33,835	17,613 21,362 6,579 11,051	3,072 11,916 1,748 3,505	19,866 12,710 5,654 9,301	205 265 206 404	0 0 0 270	819 1,854 103 539	205 794 1748 809	1,024 530 1,439 2,426	0 0 0 0	0 0 0 0	0 0 0 0	819 0 308 404	7,373 7,414 2,361 2,831	8,806 6,885 1,542 2,022	0 0 0 0
16	69	F	Hodgkin's disease	4.0	15.4	Ia Ib IIa IIb	39.2 43.2 52.6 46.6	18,891 20,215 27,036 24,698	5,018 7,171 7,151 7,829	1,254 2,160 2,314 1,025	5,006 5,357 6,102 4,763	392 316 316 93	0 173 105 93	392 518 526 559	1333 778 947 1308	2,117 1,987 631 2,330	0 0 0 0	0 0 0 0	0 0 105 0	0 346 316 0	3,136 2,333 4,103 1,491	1,568 1,728 2,916 2,330	0 86 0 0
17	39	F	Hodgkin's disease	4.0	23.0	Ia Ib IIa IIb	85.0 107.0 130.0 96.8	50,150 64,200 65,780 59,629	9,520 18,190 28,600 16,650	510 428 3,380 1,162	17,850 11,984 17,420 10,618	850 612 1,040 0	310 214 0 387	1,530 612 2,080 774	170 856 5,460 1355	2,040 6,206 5,460 3,291	0 0 0 0	0 0 1560 387	170 214 0 0	0 0 0 0	1,700 2,140 2,600 908	170 1,284 1,040 1,549	0 0 0 0
18	60	F	Gangrenous cholecystitis with pernicious anemia	1.8	7.9	Ia Ib IIa IIb	10.8 36.2 30.6 22.8	7,060 2,180 11,566 8,299	1,703 409 2,635 1,003	79 74 586 228	2,059 74 5,197 2,231	0 0 0 0	0 25 73 137	0 12 0 46	277 62 0 137	1,861 645 3,367 2,827	0 0 0 0	0 0 146 46	0 112 732 547	2,574 939 6,368 4,101	2,297 645 3,953 2,508	515 62 1076 681	

[illegible]

8 times its probable error. For each group the deviations were greater from the mean of four counts than of two counts but in no case was the difference statistically significant.

TABLE 2.—THE MEAN AND STANDARD VARIATIONS OF THE TOTAL NUCLEATED CELL COUNT AND NUMBER OF POLYS IN SEVERAL GROUPS OF DISEASES

Group	No. of samples	Mean nucleated white cell count \pm P.E.	Standard deviation \pm P.E.	Mean number of mature polys \pm P.E.	S.D. \pm P.E.
Blood-forming organs	56	62,588 \pm 2292	25,426 \pm 1620	22,443 \pm 1595	17,696 \pm 1128
Locomotor system	8	46,523 \pm 5713	23,956 \pm 4039	13,238 \pm 1571	6,588 \pm 1111
Nervous system	12	65,600 \pm 8571	44,020 \pm 6061	18,553 \pm 2495	12,812 \pm 1764
Infectious diseases	16	63,688 \pm 3331	19,756 \pm 2356	15,812 \pm 685	4,065 \pm 485
Miscellaneous	12	33,508 \pm 2392	12,287 \pm 1692	14,840 \pm 905	4,650 \pm 640
Total	104	58,513 \pm 2891	43,571 \pm 2038	19,388 \pm 1095	16,560 \pm 774

TABLE 3.—THE STANDARD DEVIATIONS FROM THE MEAN WHITE CELL COUNT OF 2 AND 4 SAMPLES FROM THE SAME PATIENT

Group	Total white cells		Difference \pm P.E.	Difference/P.E. diff.
	S.D. \pm P.E. (pairs)	S.D. \pm P.E. (quartettes)		
Blood-forming organs	9,583 \pm 611	11,619 \pm 740	-2035 \pm 960	2.1
Locomotor system	11,281 \pm 1992	18,703 \pm 3153	-7422 \pm 3683	2.0
Nervous system	22,533 \pm 3102	23,503 \pm 3236	- 970 \pm 4483	0.2
Infectious diseases	14,146 \pm 1687	15,957 \pm 1903	-1811 \pm 2542	0.7
Miscellaneous	3,533 \pm 486	6,458 \pm 889	-2924 \pm 1013	2.9
Total	12,250 \pm 573	14,399 \pm 673	-2149 \pm 884	2.4

TABLE 4.—THE STANDARD DEVIATIONS FROM THE MEAN NUMBER OF POLYS IN 2 AND 4 SAMPLES FROM THE SAME PATIENT

Group	No. of polys.		Difference \pm P.E.	Difference/P.E. diff.
	S.D. \pm P.E. (pairs)	S.D. \pm P.E. (quartettes)		
Blood-forming organs	4570 \pm 291	6296 \pm 401	-1726 \pm 495	3.5
Locomotor system	3487 \pm 588	4942 \pm 833	-1456 \pm 1020	1.4
Nervous system	5152 \pm 709	7085 \pm 976	-1934 \pm 1206	1.6
Infectious diseases	2975 \pm 355	3229 \pm 385	- 254 \pm 524	0.5
Miscellaneous	1490 \pm 205	2406 \pm 331	- 916 \pm 390	2.4
Total	4107 \pm 192	5594 \pm 262	-1487 \pm 325	4.6

Similar deviations for the mean number of polys are given in Table 4 and here, although the variation was less, the indications are not as clear. For the diseases of the blood-forming organs the standard deviation from the mean of two counts from the same sample was 4570 \pm 291 polys and for four counts from 2 samples 6296 \pm 401 polys, with a difference of -1726 \pm 495 which is 3.5 times the probable error and probably not significant. However, for the total 104 counts the standard deviations from the mean of the two counts from the same sample was 4107 \pm 192 and from the mean of the four counts 5594 \pm 262 and in this case the difference 1487 \pm 325 is 4.6 times the probable error or almost certainly significant. In other words, series of four counts from 2 samples taken simultaneously from the same patient may be significantly more variable than two counts from 1 sample in the number of observed polys. Since the number of polys is a factor in the total count and although

two counts from a single sample tend to be more alike than four counts from 2 samples taken simultaneously, sufficient variation was observed in the four counts to lessen considerably the dependence which could be placed on a single quantitative estimate of the number of cells in a single sample. These findings would indicate, therefore, that the validity of quantitative marrow determinations is very questionable. Consequently, it seems inadvisable to continue the use of detailed quantitative data or indices in conjunction with sternal marrow findings.

While demonstrating the fallacies associated with the existent quantitative marrow methods, it is certainly not our intention to belittle, or detract from the importance of sternal puncture or the vital rôle it plays in the establishment of hematologic diagnoses. However, the marrow should be studied just as the pathologist studies a tissue. To facilitate this, the material aspirated by sternal puncture should be centrifuged, and smears made of the buffy coat. Thus a tissue-like preparation is produced which can be studied just like a thin section.

The cellularity of the marrow can be estimated roughly by doing a total nucleated count on the aspirated marrow mixture or by examining the thickness of the buffy coat on the centrifuged specimen. Occasionally doubtful cases arise in which a topographic study of the marrow is necessary to supplement the information derived from sternal puncture. Then a small button of bone can be removed from the sternum by trephine⁵ and from this thin sections may be cut. Since this is an actual piece of tissue, quantitative studies of cell types as well as bone marrow histology are permissible. This procedure is much more formidable, however, than sternal puncture, and in most cases qualitative studies as outlined above are adequate. The qualitative study of sternal marrow as advocated here naturally precludes laboratory technicians doing anything but the preparation and staining of the smears, and the total cell counts. Examination of the stained marrow preparations requires the attention of an experienced hematologist, whose judgment must naturally be tempered by a thorough clinical examination of the patient.

Conclusions.—1. A quantitative study of a series of multiple sternal marrow samples was undertaken.

2. Statistical analysis indicates that quantitative determinations on aspirated marrow samples are inaccurate.

3. Qualitative marrow studies are invaluable in establishing hematologic diagnoses.

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THE SURVIVAL AFTER TRANSFUSION OF HUMAN ERYTHROCYTES THAT HAVE BEEN STORED IN CITRATE-GLUCOSE

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In previous reports we described our observations on the keeping qualities of citrated human blood stored at 4° to 6° C.,² the survival after transfusion of red cells so stored,³ and the keeping qualities of citrated human blood to which glucose has been added.⁴ The present report,* the fourth and last of the series, describes the survival, after transfusion, of red blood cells preserved with the aid of glucose.

Method. Blood was collected in 20% dihydric sodium citrate to make a final concentration of 0.4%, and glucose, 5.4% in water, was added in quantity equal to half the volume of blood. Flasks were kept undisturbed at 4° to 6° C. The life span of the erythrocytes after entering the recipients' circulation was determined by a modification of Ashby's method of non-agglutinable cell counts, as in our previous study.

Chart 1 shows the individual survival curves of 12 bloods. The numbers at the end of the curves indicate the days each blood was stored prior to use. The amount of the transfusions was 500 cc. (glucose not counted) with 2 exceptions of 750 cc. and 1000 cc.

In Chart 2 the data of the present study and that of the former study on the survival of red cells of citrated blood (containing no glucose) have been combined for the sake of contrast. Citrated cells are represented by the block at the left of the graph, the cells preserved by glucose the block on the right. The chart is constructed by plotting for each blood the number of storage days against the days of cell survival in the recipient. This chart shows that erythrocytes preserved with the aid of glucose remained useful to the recipient after a much larger storage period than cells simply citrated. In other words, cells stored in glucose for about 14 days survived

* The authors offer apologies for not presenting a greater number of observations. Such data are difficult to collect, and recent loss of personnel has made it impossible to carry the study further. The data, however, are adequate to demonstrate the prolonged survival of red blood cells preserved with glucose.

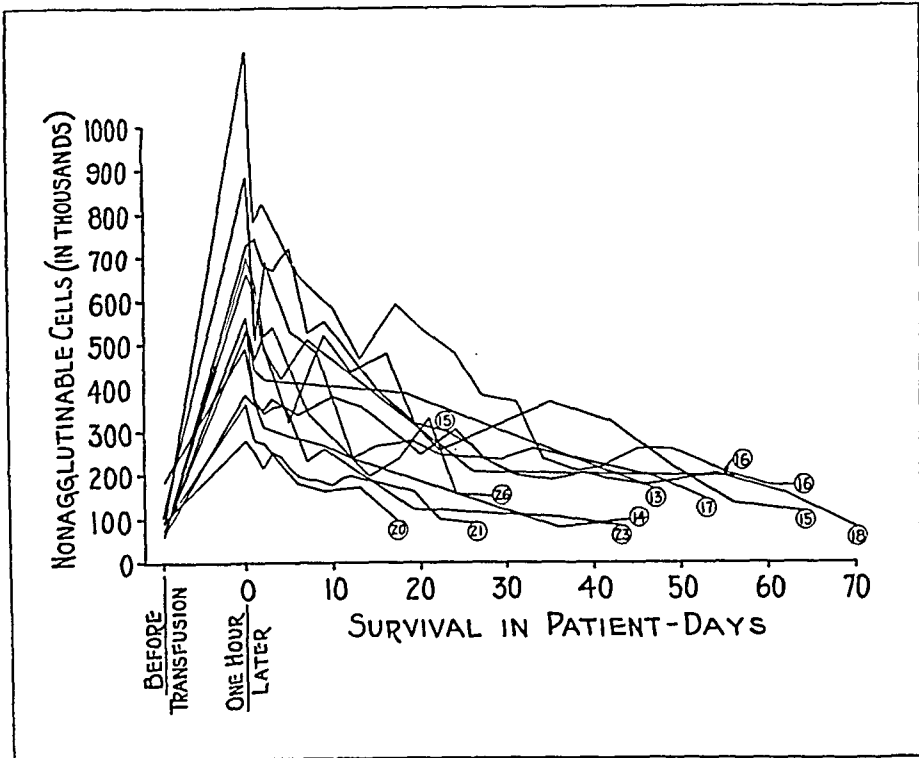


CHART 1.—Erythrocyte survival after transfusion of blood stored in citrate-glucose.

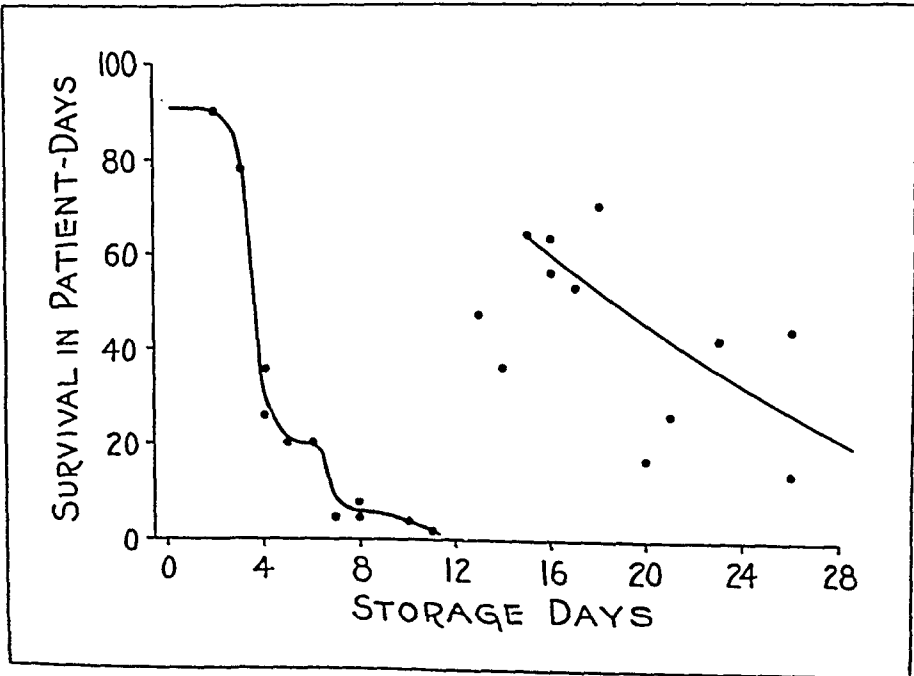


CHART 2.—Relation between storage time and survival of erythrocytes after transfusion. The observations on the left of the chart refer to citrated blood, those on the right of the chart to blood stored in citrate-glucose.

in the patient as long as citrated cells which had been stored for only 3 or 4 days. Moreover, glucose treated cells stored as long as 26 days had still not reached the "foreign body state" characteristic of citrated cells after 7 or 8 days of storage.

An observation of importance is that red cells preserved with glucose did not survive in the recipient as long as was expected from *in vitro* studies. In our third paper glucose treated cells were shown to keep for about 4 weeks before beginning to hemolyze. The graph shows, however, that the erythrocytes of blood kept 13 to 18 days survived definitely less well than those of fresh blood in the studies of Ashby¹ and of Wearn⁶ who recorded an average life span of 81 days. The fourteenth day of storage, therefore, represents the age of demonstrable deterioration, comparable to the 3 to 4 day age of citrated blood. In no instance, however, was harmless hemolysis with jaundice noted as it was after some transfusions with citrated blood. This justifies our practice of discarding blood after two weeks of storage. Had our observations included blood stored for a period briefer than two weeks, in all probability longer survival spans would have been noted. In our own bank, which supplies 50 transfusions a month, the average age of blood when used is 6 days. Consequently we feel assured that the average survival time of red blood cells preserved with glucose under conditions comparable to those in our institution is better than 50 days.

General Summary. Summarizing this entire study, it may be said that chilled citrated human blood undergoes a rapid deterioration in all its cellular and in some of its plasma components. When such blood is administered to patients the red cells survive as long as those of fresh blood provided that storage has been no longer than 2 or 3 days. With each additional day of storage, however, they become progressively less useful to the patient, and after 7 days of storage are apparently treated by the human organism as foreign bodies and are eliminated in 24 to 48 hours. The addition of glucose to citrated blood enhances its keeping properties about four times, as shown by both *in vitro* and *in vivo* studies. The erythrocytes of blood to which glucose has been added will, after storage of about 14 days, be detectable in the recipient's blood stream (where they presumably function) for about 50 days. This survival is comparable to that of citrated cells stored for 3 or 4 days. It is not, however, as long as the survival of fresh unstored cells. The clotting properties of stored blood diminish with such rapidity that it seems wise to use only fresh blood in the transfusion of those with hemorrhagic diathesis. In the treatment of sepsis a storage limit of 5 days is advisable.⁵

It seems possible that the preoccupation of the medical profession at the present time with banks, both of whole blood and of plasma, has led us to forget that fresh whole blood is easily obtainable, and that it has distinct advantages over any substitute. The blood

bank, in fact, necessitates some compromises with the very best technique of blood transfusion. These compromises are: the use of the universal donor for many patients, a practice which has resulted fatally in a small per cent of cases; the use (usually) of non-fasting donors, a practice of considerable danger to food allergic recipients; the filtering of blood, usually through gauze which imparts lint; and the use of blood which has undergone at least some deterioration in cells and in components of the plasma. We realize, of course, that the bank offers certain advantages to be set off against these objections, namely, the greater rapidity with which blood may be supplied in emergencies; the performance of tests for syphilis by skilled rather than by unskilled workers; and the avoidance of the confusion and inconvenience incident to the selecting of individual donors of fresh blood. On the whole, in routine practice in larger hospitals where blood is not stored too long, the blood bank would seem to offer more advantages than disadvantages to the average patient. Recourse, however, to fresh whole unfiltered blood of homologous type from fasting donors should still be practised in selected cases.

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BLOOD CLOT RETRACTION

II. THE SIGNIFICANCE OF THE EXTRACORPUSCULAR VOLUME OF THE CLOT AND ITS CLINICAL APPLICATION*

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THE efficiency of blood clot retraction may be measured in terms of the extracorporeal volume of the clot.¹ This is defined as the volume of the clot exclusive of its contained packed cells expressed as a percentage of the total volume of the specimen studied.

* Aided by a grant from the Christine Breon Fund and by a grant from Mr. Frank Kennedy.

Method. The upper end of a copper wire about 1 mm. in diameter is attached to a cork. The free end of the wire is bent in the shape of a hook. An arbitrary amount of venous blood, usually 5 cc., is carefully transferred to a graduated centrifuge tube and the cork and wire are fitted so that the hook is immersed in the upper layers of the specimen. After coagulation of the blood has occurred, the tube is placed in a water-bath (37° C.) for 1 hour. It is then taken from the bath and the total volume of the specimen is recorded. The clot is elevated, allowed to drain, and then removed. The clot volume is measured by subtracting the residual volume of serum from the total volume of the specimen. To obtain the volume % of the blood clot, the observed volume of the clot is divided by the total volume of the specimen and the quotient is multiplied by 100. The packed cell volume including all cellular elements is obtained by centrifugalization of the blood at 3000 r.p.m. for 30 minutes. The difference between the total packed cell volume in % and the clot volume in % is a measure of the *extracorpuscular volume of the clot*.

The authors¹ found that in 100 normal subjects the extracorpuscular mean volume measured 9.1% and the standard deviation of the sample was 7.5%; in 42 subjects who had prothrombin concentrations of 50% or less, the mean value was 18.2%, and the standard deviation was 12.4%; and in 35 subjects who had platelet counts of 200,000 or less the mean value was 38.9% and the standard deviation was 14.1%. The normal value was arbitrarily considered to fall within two standard deviations of the mean (−5.9% to 24.1%). Using this criterion, blood clot retraction was diminished in 13 of the 42 patients who had hypoprothrombinemia and in 30 of the 35 patients who had thrombocytopenia. In some patients with hypoprothrombinemia or thrombocytopenia, the blood clot may retract normally, and conversely deficient clot retraction may be observed in some patients whose platelet counts and prothrombin concentrations are normal. Furthermore, deficient clot retraction may be found in patients who do not have abnormal bleeding, while normally retracting clots are frequently seen in those who suffer from marked bleeding tendencies.

The measurement of blood clot retraction alone does not give sufficient information regarding the hemostatic equilibrium to permit any final conclusions concerning the tendency to bleed. The interpretation of the clinical significance of deficient clot retraction can be made only in the light of other hemostatic tests. Normal values for these tests are given in Table 1.

The following cases demonstrate the application of blood clot retraction measurements when considered in relation to other hemostatic tests in the study of the problem of abnormal bleeding. Cases 1 to 4 illustrate the frequent association of hypoprothrombinemia and thrombocytopenia with deficient blood clot retraction. Cases 5 and 6 demonstrate some aspects of the problem presented by the finding of deficient clot retraction in patients with normal prothrombin concentrations and normal platelet counts. Although a careful study of each patient was undertaken, only the pertinent data of each case is here recorded.

TABLE 1.—THE NORMAL VALUES FOR HEMOSTATIC TESTS

Test	Mean	2 standard deviations (σ_x)	Range
Bleeding time (Ivy) in minutes	3.2	1.4	0.4 to 6.0
Coagulation time (modified Lee and White) in minutes	8.8	2.7	3.4 to 14.2
Platelet count (Rees and Ecker) per c.mm.	422,000	87,000	248,000 to 596,000
Extracorpuseular volume of clot, %	9.1	7.5	(—) 5.9 to 24.1
Prothrombin concentration (Quick) in %	70 to 100
Capillary permeability (Dall-dorf), number of petechiæ with 200 mm. Hg vacuum pressure	0 to 10

The standard statistical method was used in setting up the limits of normality for the bleeding time, coagulation time, extracorpuseular volume of the clot and platelet count. One hundred normal subjects were studied. The limits of significance of the data were arbitrarily set at two standard deviations from the mean, which includes approximately 96% of the observations. The mean is taken at the point of reference. All measures which were calculated were at least 3 times their sampling errors. The limits of normality for the prothrombin concentration and capillary permeability were arbitrarily set by direct observation. The range of the prothrombin concentration was from 65% to 100%; 98% of the observations fell between 70% and 100%. The range of the capillary permeability was from 0 to over 30 petechiæ. There were not more than 10 petechiæ in 88% of the observations.

CASE 1. Y. S. White woman, aged 19. *Diagnosis:* idiopathic thrombocytopenic purpura.

Clinical Summary. The patient had suffered from menorrhagia from the time of menarche (aged 13) until her 17th year of age. She had had recurrent ecchymoses since her first menstrual period. The occurrence of frequent epistaxis during the past 2 years had recently been controlled by a submucous resection. She had suffered from symptoms of hypothyroidism for the past year. The spleen was not palpable. B.M.R. was -11%. Plasma cholesterol 123 mg.%. Plasma cevitic acid 1.71 mg.%. The results of the hemostatic tests were as follows:

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiæ)	Remarks
9/28/39	>30	6	75	46	75	Shower	Thyroid, 1 gr. daily. Hypothyroidism corrected, but ecchymoses continue.
10/ 6/39	>30	8½	90	52	95	Shower	
10/20/39	>30	6½	100	50	60	Shower	
10/31/39	>30	6	75	53	70	Shower	Moccasin snake venom therapy from 10/31/39 to 7/26/40 without significant effect. Ecchymoses continue.
11/ 3/39	>30	8	85	60	95	Shower	
12/ 4/39	>30	7	75	60	100	Shower	
3/ 9/40	>30	11½	100	43	110	28	
3/21/41	>30	11½	100	44	110	Shower	

The results of the hemostatic tests performed on this patient illustrate the characteristic findings associated with thrombocytopenia. The bleeding time was prolonged, the coagulation time and prothrombin concentration were normal, the capillary permeability and the extracorpuseular volume % of the clot were markedly increased.

CASE 2. L. D. White girl, aged 12. *Diagnosis:* dysovarian purpura.

Clinical Summary. The patient had experienced the onset of petechiæ and purpuric maculæ 4 days before hospitalization. The spleen was not palpable.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiae)	Remarks
1/ 8/41	>30	10	80	31	70	6	Body covered with petechiae and purpuric maculae.
2/24/41	7	7	90	12	450	No	All petechiae and purpuric spots disappeared with 1st menstrual period 2 weeks after first observation.
3/20/41	3½	10	95	18	490	2	No further bleeding.

The results of the hemostatic tests demonstrate a diminution in the bleed-ing time and in the extracorporeal volume of the clot coinciding with recovery from the underlying condition.

CASE 3. M. F. White man, aged 55. *Diagnosis:* portal cirrhosis of the liver.

Clinical Summary. Two months before our observation the patient noted the onset of ascites, slight jaundice, fatigue and loss of weight. He had also had frequent severe epistaxis for a period of 2 weeks. The liver was enlarged 4 cm. below the right costal margin. The spleen was not palpable. The rose bengal test showed marked impairment of biliary excretory function (8 minutes 100%, 16 minutes 90%). Serum proteins: total 8%, albumin 1.46%, globulin 6.54%. Plasma cevamic acid, 1.4 mg.%. Plasma fibrinogen 0.22%.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiae)	Remarks
3/26/40	4½	6	30	34	360	No	Recurrent epistaxis.
4/ 1/40	6	5½	30	40	180	No	5 mg. 5-amino-2-methyl naphthol HCl intravenously.
4/ 2/40	5½	7½	30	45	270	No	Condition unchanged.
4/ 3/40	5	8	30	52	210	No	Epistaxis continues.

The results of the hemostatic tests in this case demonstrate the association of impaired clot retraction with hypoprothrombinemia in a patient suffering from advanced cirrhosis of the liver. The administration of vitamin K failed to alter either the hypoprothrombinemia or the extracorporeal volume of the clot.

CASE 4. M. M. White woman, aged 65. *Diagnosis:* cholangitis with partial obstructive jaundice, multiple pyogenic abscesses of the liver.

Clinical Summary. During the 3 weeks preceding our observation the patient had suffered from right upper abdominal pain, slight jaundice, intermittent fever, dark colored urine and light colored stools. For 1 day she had had recurrent profuse epistaxis, which could not be controlled by repeated nasal packs. Icterus index 75. Plasma fibrinogen 0.87%.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiae)	Remarks
9 A.M. 3/3/40	7½	18	3	35	380	No	Profuse epistaxis. Given 5 mg. 4-amino-2-methyl naphthol hydrochloride I.V.
5 P.M. 3/ 3/40	1	6	30	25	—	No	Epistaxis stopped and nasal packs were removed 1 hour after vitamin K.
9 A.M. 3/ 4/40	1	4½	75	15	—	No	No further epistaxis. Died 1 hour later.

The results of the hemostatic tests in this case demonstrate improvement in clot retraction coinciding with a remarkable elevation of the prothrombin concentration following the administration of vitamin K.

CASE 5. A. M. White woman, aged 19. *Diagnosis:* thrombocytopenic purpura.

Clinical Summary. The patient was first seen on January 25, 1939, with complaints of marked gingival bleeding, epistaxis, ecchymotic areas on the buccal mucosa and pharynx, purpuric spots in the conjunctivæ, petechial hemorrhages scattered over the body and splinter hemorrhages under the nails of the fingers and toes of 1 months' duration. The spleen was palpable 2 finger breadths below the left costal margin. Bleeding time (Duke), greater than 20 minutes. Platelet count (Rees and Ecker) 80,000 per c.mm. Capillary permeability (Dalldorf) markedly increased. Plasma vitamin C 0.48 mg.%. During 1 week of hospitalization, she was started on a course of moccasin venom therapy, her symptoms gradually abated, and her spleen became impalpable. The platelet count varied between 80,000 and 120,000 per c.mm. She remained almost asymptomatic for 10 days, then suffered a recurrence of purpuric manifestations, including menorrhagia. At this time her platelet count was 80,000. During the following 3 weeks she was given Roentgen therapy to the spleen (total of 1200 r to each of 3 areas), all of her purpuric symptoms disappeared and her platelet count rose to 300,000 per c.mm. She had no symptoms of purpura for the next 6 months. In September and October, 1939, she noted on several occasions, small areas of petechial hemorrhages, and during these months her platelet count varied between 180,000 and 260,000 per c.mm. Since that time she has been entirely free of purpura and her platelet counts have varied between 290,000 and 400,000 per c.mm.

Unfortunately blood clot retraction measurements were not done until the patient was recalled specifically for this purpose in September, 1941. The results of the hemostatic tests were as follows:

Date	Bleeding time (min.)	Coagulation time (min.)	Prothrombin concentration (%)	Extracorpuscular vol. of clot (%)	Platelet count (thous. per c.mm.)	Capillary permeability (petechiæ)
9/17/41	4	7	70	29	320	No
9/27/41	3	9½	70	34	360	No

Because of the previous thrombocytopenia, it might be assumed that the deficient clot retraction observed in the blood of this patient was due to a defective clot retractive function of the platelets, since poor clot retraction persists despite an elevation of the platelet count to normal numbers. The assumption of "thrombasthenia" in this patient is strengthened by the recent occurrence of thrombocytopenia in her sister, who has suffered from petechial hemorrhages, ecchymoses, gingival bleeding, and menorrhagia for the past five months. In the latter, the bleeding time has varied between 14½ and over 30 minutes, the coagulation time between 8 and 12½ minutes, the prothrombin concentration between 65% and 100%, the extracorpuscular volume of the clot between 16% and 49%, and the platelet count between 80,000 and 190,000 per c.mm. The capillary permeability has been increased on all occasions.

CASE 6. J. F. Male, aged 29. *Diagnosis:* atypical thrombocytopenic purpura.

Clinical Summary. The patient had bruised easily and had suffered from frequent epistaxis since childhood. For the past year the epistaxes had increased in frequency, fresh blood had been noted in the stool on many occasions, and there had been recurrent showers of large petechial hemorrhages over his lower extremities. Epistaxis had been intractable for the past month. An indolent ulcer had been present over his left tibia for the

past 10 years. Nine years previously, after the third of a series of salvarsan injections, which had been given in an attempt to heal the ulcer, he had developed toxic hepatitis, which had persisted for 4 months. The family history was negative except that the father had had frequent epistaxis. On entry to the hospital the patient was found to have generalized purpura, most marked on the lower extremities. There were many bleeding points on Kiesselbach's area in the right nostril. The oral and pharyngeal mucous membranes were spotted with many small hemorrhages. Prolapsed bleeding hemorrhoids were present. The spleen was palpable 2 fingerbreadths below the left costal margin on deep inspiration. There were many red blood corpuscles in the urine. Plasma fibrinogen 1.17%. Serum calcium 9.8 mg. %.

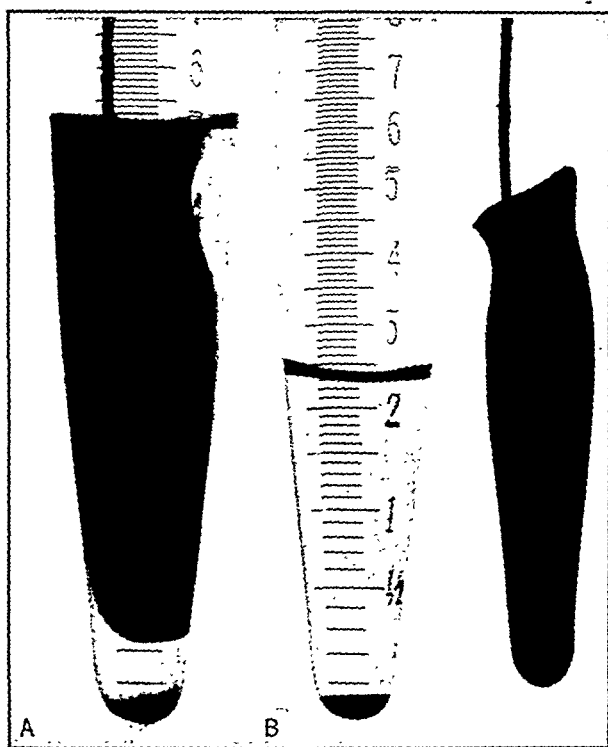


FIG. 1.—The appearance of the blood clot in a normal subject. Prothrombin concentration 100%. Platelet count 480,000 per c.mm. Serum volume 43%. Clot volume 57%. Packed cell volume 39. Extracorporeal volume of clot 18%. While this clot is within normal limits for a patient with this packed cell volume, it would be quite abnormal if the packed cell volume were 16 as in Figure 2. In that case the extracorporeal volume of the clot would be 41%.

While in the hospital, the patient bled into the right maxillary sinus, into the tissues of the neck, and under the right parietal pleura. He died on January 8, 1942, and at autopsy there was found bilateral cavernous sinus thrombosis and subarachnoid hemorrhages.*

* Further details regarding the coagulation defect and autopsy findings in this patient will be published at a later date.

The results of the hemostatic tests were as follows:

Date	Bleeding time (min.)	Coagulation time (min.)	Prothrombin concentration (%)	Extracorpuscular vol. of clot (%)	Platelet count (thous. per c.mm.)	Capillary permeability (petechiæ)
12/ 5/41	>30	24	75	51	70	Shower
12/24/41	10½	42	40	44	160	2
12/30/41*	>30	105	45	43	230	4
1/ 2/42	>30	175	70	43	250	No
1/ 6/42	>30	130	80	44	180	10

* 2 mg. Synkamin (4-amino-2-methyl-naphthol) were given daily by the intravenous route.†

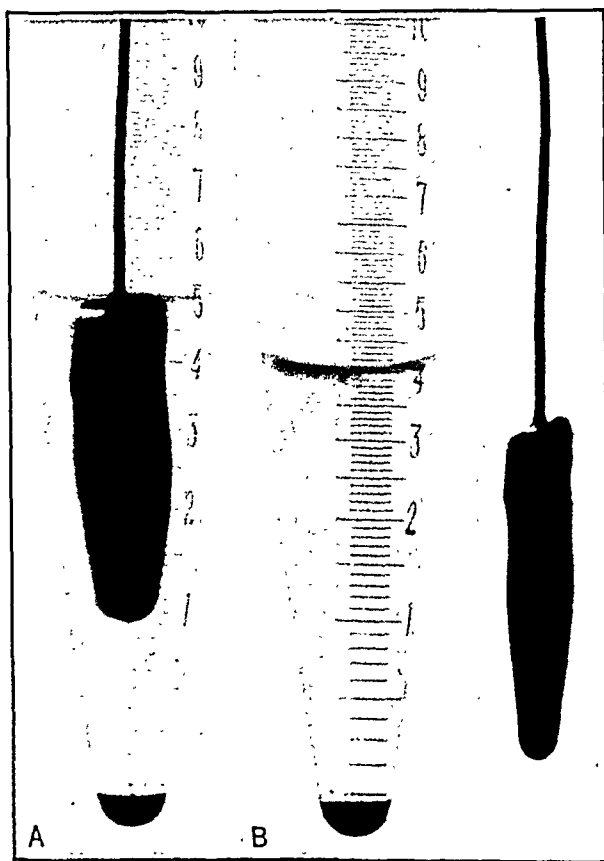


FIG. 2.—Normal clot retraction in a patient with pernicious anemia. Prothrombin concentration 65%. Platelet count 400,000 per c.mm. Serum volume 80%. Clot volume 20%. Packed cell volume 16. Extracorpuscular volume of clot 4%.

Between December 9 and December 20, 1941, the patient was given Roentgen therapy to the spleen (a total of 1200 r to each of 2 areas). During the following 3 weeks daily platelet counts varied between 120,000 and 250,000. Despite the elevation of the platelet count to the lower limits of normal, the degree of clot retraction remained unchanged and the coagulation time continued to be markedly prolonged. It was observed on the blood smear that the platelets were large, darkly staining and did not contain any granules.

Regardless of their numbers, the platelets in this patient were deficient both in their clot retractive function and in their ability to supply thromboplastin for the processes of coagulation of the blood.

† Kindly furnished by Parke, Davis & Company, Detroit, Mich.

Discussion. The blood clot is made up of cells, a fibrin meshwork and serum. The extracorporeal volume of the clot is composed chiefly of serum occluded within the clot. The packed cell volume must be known in order to calculate the extracorporeal volume of the clot. The appearance of normal clot retraction in a subject whose packed cell volume was 39 is shown in Figure 1, and of normal clot retraction in a patient whose packed cell volume was 16 in

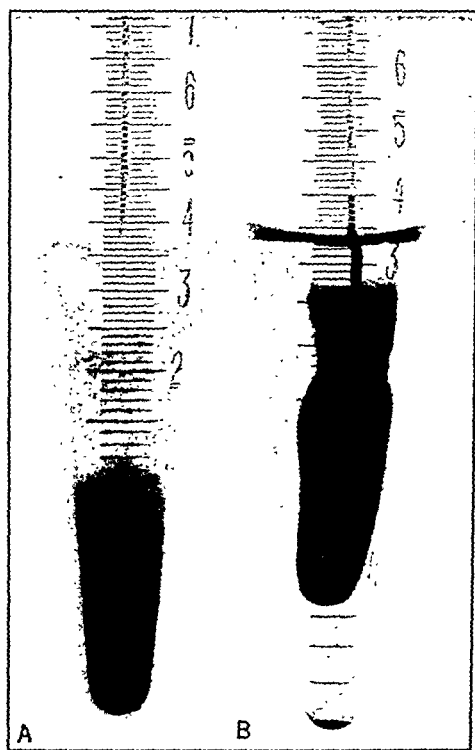


FIG. 3.—The appearance of the blood clot in a patient with obstructive jaundice. A, With hypoprothrombinemia—prothrombin concentration 10%. Serum volume 35%. Clot volume 65%. Packed cell volume 14. Extracorporeal volume of clot 51%. B, The clot of the same patient after correction of hypoprothrombinemia following the administration of vitamin K. Prothrombin concentration 90%. Serum volume 72%. Clot volume 28%. Packed cell volume 13. Extracorporeal volume of clot 15%.

Figure 2. While clot retraction in both of these patients was within normal limits for the respective packed cell volumes, it should be noted that had the volume of the clot in the second patient been the same as that observed in the first, the extracorporeal volume would have been 41% rather than 4% and decidedly pathological. The appearance of deficient clot retraction in a patient with hypoprothrombinemia due to obstructive jaundice before the administration of vitamin K is shown in Figure 3A, and of normal clot

retraction in the same patient after its administration in Figure 3B. Markedly deficient retraction of the clot of a patient with thrombocytopenia is shown in Figure 4.

In addition to the volume of the packed cells and the quantity and quality of the prothrombin and platelets, it is conceivable that clot retraction may be influenced either by fibrinogenopenia, an extremely rare condition, or by the inability of the formed fibrin

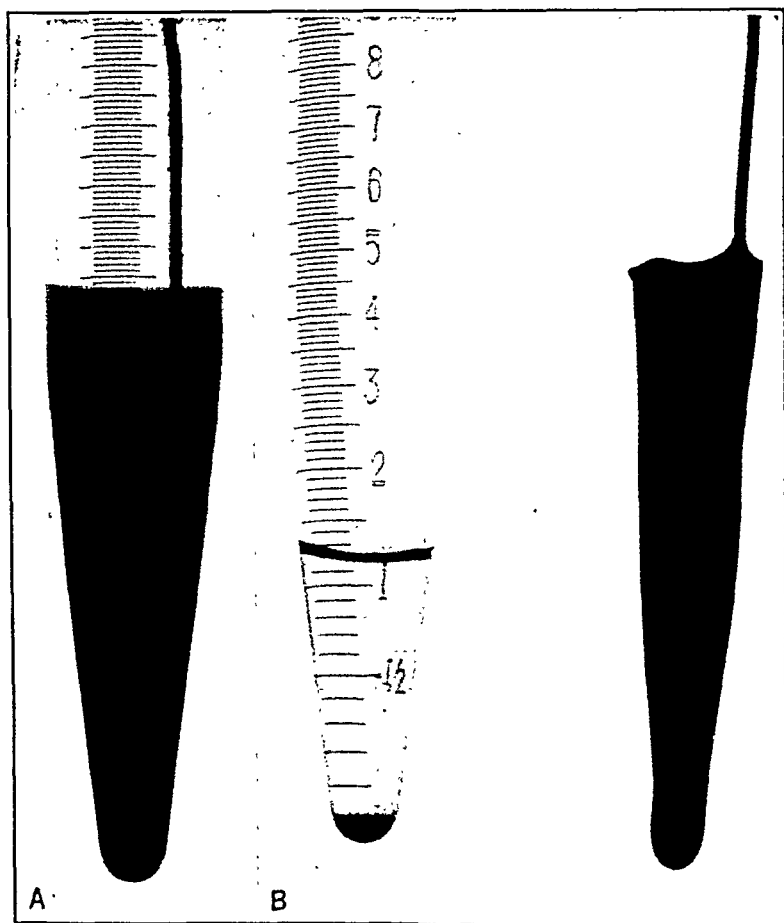


FIG. 4.—The appearance of the blood clot in a patient with thrombocytopenia (aplastic anemia). Prothrombin concentration 60%. Platelet count 70,000 per c.mm. Serum volume 24%. Clot volume 76%. Packed cell volume 26. Extracorpuseular volume of clot 50%.

to behave in the normal manner. The latter condition might be called "fibrinasthenia." However, there would be no way to prove the existence of such a disorder. In addition, it has been shown that blood clot retraction may be profoundly influenced *in vitro* by the addition of various amino acids.² Hence, there may be metabolic defects resulting in excesses in the blood stream of substances which promote or inhibit clot retraction. It may be that deficient clot retraction is due in some instances to what has been termed

"thrombasthenia" (Glanzmann), a condition in which the platelets although present in normal numbers are said to be deficient in their clot retracting ability. It would be difficult to prove or disprove the existence of such a condition. Some information could perhaps be obtained by *in vitro* experiments with isolated platelets. Certainly it must be conceded that the finding of deficient blood clot retraction in the presence of a normal platelet count does not prove the existence of "thrombasthenia." We have made some clinical observations (see Cases 5 and 6) in which one might infer that in certain instances the platelets, although present in normal numbers, may be the cause of deficient blood clot retraction.

Summary. An accurate measurement of the degree of blood clot retraction is desirable in the study of patients suffering from hemorrhagic disorders. Diminished clot retraction is often seen in conjunction with hypoprothrombinemia and is frequently observed in patients with thrombocytopenia. It may be present when neither of these conditions obtains. One cannot assume under the latter circumstances that "thrombasthenia" is present, as other conditions, including fibrinogenopenia, "fibrinasthenia" or the presence of circulating clot retraction-inhibiting substances, may likewise be responsible for diminished clot retraction. There is some clinical evidence to support the hypothesis that under certain circumstances one may be justified in assuming that a condition of "thrombasthenia" may exist.

We take this opportunity to thank the staff members of the Division of Pediatrics, University of California Medical School for permission to report the data on Case 2.

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CALCAREOUS AORTIC STENOSIS IN A CASE OF DEXTROCARDIA WITH SITUS INVERSUS

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TRANSPOSITION of the viscera is an uncommon condition. LeWald³ recorded its clinical incidence as 1 in 35,000 physical examinations of recruits for the U. S. Army. Considerably more infrequent, however, is the association of congenital dextrocardia with acquired lesions of the cardiovascular system.

In 1911 Owen⁵ reported a case of situs inversus in which mitral stenosis involved the transposed heart. Willius⁶ in 1931 described

dextrocardia with situs inversus complicated by hypertensive heart disease. The electrocardiogram in the latter case showed changes indicative of strain of the left ventricle. In 1938 Crawford and Warren¹ reported dextrocardia with situs inversus associated with coronary thrombosis. Electrocardiographic studies revealed an infarct in the posterior wall of the left ventricle. In the same year Manchester and White⁴ recorded transposition of the viscera complicated by hypertensive and coronary heart disease. The electrocardiogram showed changes compatible with myocardial disease. More recently, King² has described the association of situs inversus with syphilitic aortitis and aortic insufficiency.

The purpose of this paper is to present a case of congenital dextrocardia complicated by calcareous aortic stenosis which, as far as can be ascertained, has not been previously recorded.

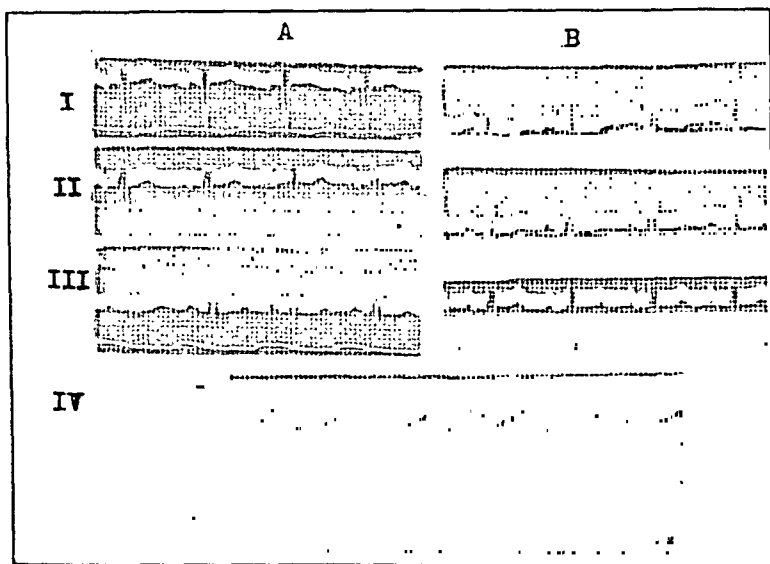


FIG. 1.—A, Routine Leads I, II, III, IV; B, with electrodes reversed in the limb leads to correct for the dextrocardia.

Case Report. G. J., a 43-year-old Swedish merchant seaman, was admitted to the hospital on September 15, 1941, because of nocturnal dyspnea and cough of 1 week's duration. He had been well until 3 weeks prior to entry when he experienced marked dyspnea on exertion and aching pain in the right mammary region. Edema of the ankles became evident shortly after the onset of symptoms. From the age of 15 he engaged in laborious occupations without limitation of activities. He stated that he had had a serious lung or heart ailment in 1907 and gonorrheal urethritis in 1938. There was no history of syphilis or rheumatic fever.

Examination revealed a well-nourished and well-developed adult white male who was dyspneic, orthopneic and cyanotic. There was a linear birthmark in the midline of the forehead. The veins in the neck were prominent and pulsating. Temperature was 99.4° F, pulse 96, respirations 30. The radial pulses were of small volume, equal and regular. The blood pressure was 110, 85. The apex impulse of the heart was felt in the sixth right intercostal space in the anterior axillary line. There was a marked systolic thrill



FIG. 2.—Roentgenogram showing dextrocardia with marked enlargement of the heart.
“Gas bubble” in stomach is seen on right side.

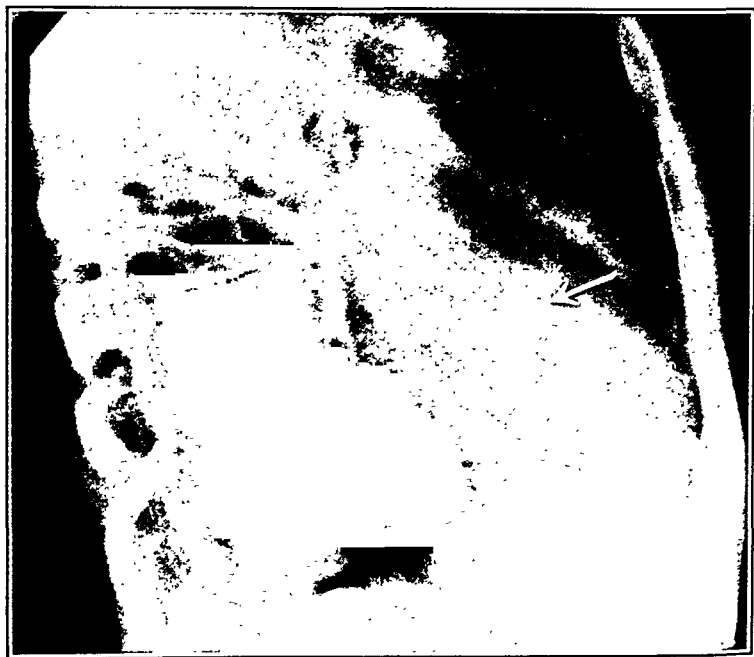


FIG. 3.—Roentgenogram, lateral view, showing calcification in the aortic valve.

in the second and third intercostal spaces to the left of the sternum. A loud harsh systolic murmur was heard with maximal intensity in this area and to a lesser degree over the entire precordium and neck vessels. The aortic second sound was absent and replaced by a short faint diastolic murmur. There was dullness at both lung bases posteriorly, with moist râles throughout the lower lobes. The liver was situated on the left side, its border being palpable 3 fingerbreadths below the costal margin. The spleen was not felt. There was marked edema of the lower extremities.

The blood Wassermann and Kahn reactions were negative.



FIG. 4.—Dextrocardia with situs inversus.

Electrocardiogram (Fig. 1A) shows normal rhythm with a ventricular rate of 90; P and QRS waves inverted in Lead I; T waves upright in all leads and slight elevation of the S-T segment in Lead I; P-R interval 0.15 sec., QRS interval .07 sec.; marked right axis deviation.

A roentgenogram of the chest reveals the maximum heart measurements as 10.8 cm. to the right and 7 cm. to the left, the transverse diameter of the chest being 28.4 cm. The lateral view shows a dense shadow in the region of the aortic valve suggestive of calcification.

Fluoroscopic examination with the aid of barium taken by mouth demonstrated complete situs inversus viscerum.

Following bed rest and digitalization the condition of the patient improved until October 28, when there was a sudden onset of knifelike pain in the lower left chest with elevation of temperature to 101° F. Expectoration of bloody sputum developed on the following day. Roentgen ray of the chest revealed evidence of an infarct at the base of the left lung. Dyspnea increased and necessitated the use of an oxygen tent. Mild icterus developed. Subsequent chest films showed multiple infarcts throughout both lungs. Patient failed to respond to therapy and died on December 20.

Postmortem Examination. There was complete transposition of all the thoracic and abdominal viscera. The parietal epicardium was smooth and glistening. The visceral epicardium presented large plaques of milky discoloration and thickening. The heart (wt. 810 gm.) was markedly enlarged downward and to the right. The right auricle was moderately dilated and its wall was thin. Upon opening the chambers of the heart the mural endocardium appeared ordinary. The foramen ovale was closed. The mitral, tricuspid, and pulmonary valves showed no lesions and their orifices were of normal size. The aortic orifice showed marked stenosis and admitted an instrument 1 cm. in diameter with difficulty. The aortic cusps were fused and completely replaced by spikelike calcareous masses. The aortic ring showed slight thickening with focal deposits of calcareous material. The left ventricle averaged 25 mm. in thickness, and the right 6 mm. There was great hypertrophy of the papillary muscles. The aorta



FIG. 5.—Calcareous stenosis of the aortic valve in "mirror image" dextrocardia.

was of slightly smaller caliber than normal. Its wall was thin and elastic and revealed no significant pathologic changes. The arteries arising from the aorta, as well as those throughout the body, showed complete reversal of their normal position. The left lung weighed 1120 gm., the right 1000 gm. There were 3 lobes in the left lung and 2 in the right. Numerous large infarcts were present throughout both lungs. On section old and recent infarcted areas were noted. The intervening parenchyma was waterlogged. The liver presented an advanced nutmeg appearance.

The cardiac findings were compatible with a rheumatic etiology.

Discussion. The diagnosis of situs inversus was made on the basis of physical findings, the visualization of the transposed heart, stomach and liver by Roentgen ray, and the inversion of the P waves in Lead I of the electrocardiogram.

Stenosis of the aortic valve was recognized from the classical signs of systolic thrill and murmur in the aortic area (in this case the second left interspace), absent second aortic sound, narrow pulse pressure and small pulse. The configuration of the heart and the demonstration of calcification in the region of the aortic valve on the roentgenogram supported this impression.

The electrocardiograms are of interest since they differ from those obtained in uncomplicated situs inversus. In the latter there is

total inversion of Lead I and transposition of Leads II and III. When the electrodes in the limb leads are reversed to correct for the dextrocardia, a normal electrocardiogram is obtained. In this case, however, the effect of the acquired valvular lesion was superimposed upon that of the congenital anomaly. Thus there is unusually marked right axis deviation, slight elevation of the S-T segment in Lead I and upright T wave in Lead I. With reversal of the electrodes, one observes left axis deviation and slight depression of the S-T segment with inversion of the T wave in Lead I, a record indicative of strain of the left ventricle (Fig. 1B).

Summary. A case is presented in which calcareous aortic stenosis (rheumatic?) was found in a 43-year-old male with situs inversus. Electrocardiograms showed the effect of the conditions cited. We have found no similar case reported.

The authors wish to acknowledge the assistance of Dr. J. G. Pasternack who performed the postmortem examination.

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METABOLIC STUDIES ON NEOPLASM OF BONE WITH THE AID OF RADIOACTIVE STRONTIUM*

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CHEMICAL and spectrographic studies regarding the mineral composition of the animal body have revealed the presence of "trace" amounts of strontium in living tissue. Stoeltzner⁹ has reported the first description of this by König in 1874 and her own experiment of feeding dogs with strontium. She found a selective uptake in the spongiosa and in the epiphyseal regions of the bones. Growing animals which were maintained on a diet low in calcium and in which the normal calcium requirement was replaced by strontium devel-

* This work has been carried out through the support of the Rockefeller Foundation and the Columbia Fund for Medical Physics.

oped toxic symptoms clinically resembling rickets. The strontium-fed animals showed a considerably higher amount of water-soluble alkaline earth content in the bones than is found in rickets, and therefore a biochemical difference between the two elements was apparently demonstrated. Lehnerdt⁴ found that a part of ingested strontium was excreted in the milk. He also found a considerable amount in the bones of suckling young. According to McCollum,⁵ Wheeler (loc. cit.) found that strontium was capable of replacing calcium to a considerable extent in the eggshell and in the bones. Shipley (loc. cit.) and coworkers pointed out that this mineral cannot replace calcium in normal bone formation. Kenney and McCollum (loc. cit.) confirmed these observations. Drea (loc. cit.) showed that strontium is one of the elements which pass from the food and water into the hen's blood and egg, and then into all of the tissues of the embryo.

The cyclotron (Lawrence *et al.*³) has made available a supply of the radioactive isotopes of calcium ($^{45}_{20}\text{Ca}$) and strontium (Sr^{89}). By means of these Pecher^{1,6a,7} was able to resolve the results of classical investigations into a quantitatively accurate formulation of the exchange of calcium and strontium. He found that:

1. Of a dose of radioactive calcium, 58% was recovered from the skeletons of mice after 24 hours. Of a dose of radioactive strontium, 33% was similarly recovered.⁶

2. In the case of both radioactive strontium and radioactive calcium the activity of the skeletons of mice indicated that nearly maximum uptake was reached 8 hours after intravenous administration.⁶

3. Bone uptake of radioactive calcium and radioactive strontium was nearly three times as great following intravenous administration as that following oral administration.⁶

4. Radioactive calcium and strontium originally fixed in the skeletons of mice was found to migrate to the fetuses during the last days of pregnancy and to be transferred to offspring through lactation.⁷

5. Radio-strontium administered intravenously to lactating cows was recovered in the milk in the amount of about 10% of the dose, during the first $4\frac{1}{2}$ days following administration.¹

The demonstration of the selective localization of calcium and strontium in bone has suggested strongly the application of the radioactive isotopes of these minerals to clinical metabolic studies and possibly to therapeutic bone irradiation. Because of its relatively greater availability radioactive strontium has been selected for this purpose. Pecher^{6b} has reported clinical and postmortem studies with radioactive strontium on a group of cases of carcinoma with demonstrated bone metastases.

Figure 1 demonstrates the method of treatment usually employed in these cases. Response of the red blood cell level is shown. The

lowering of the phosphatase* value and its maintenance at a point only slightly above the normal limit over a considerable period of time is also indicated.

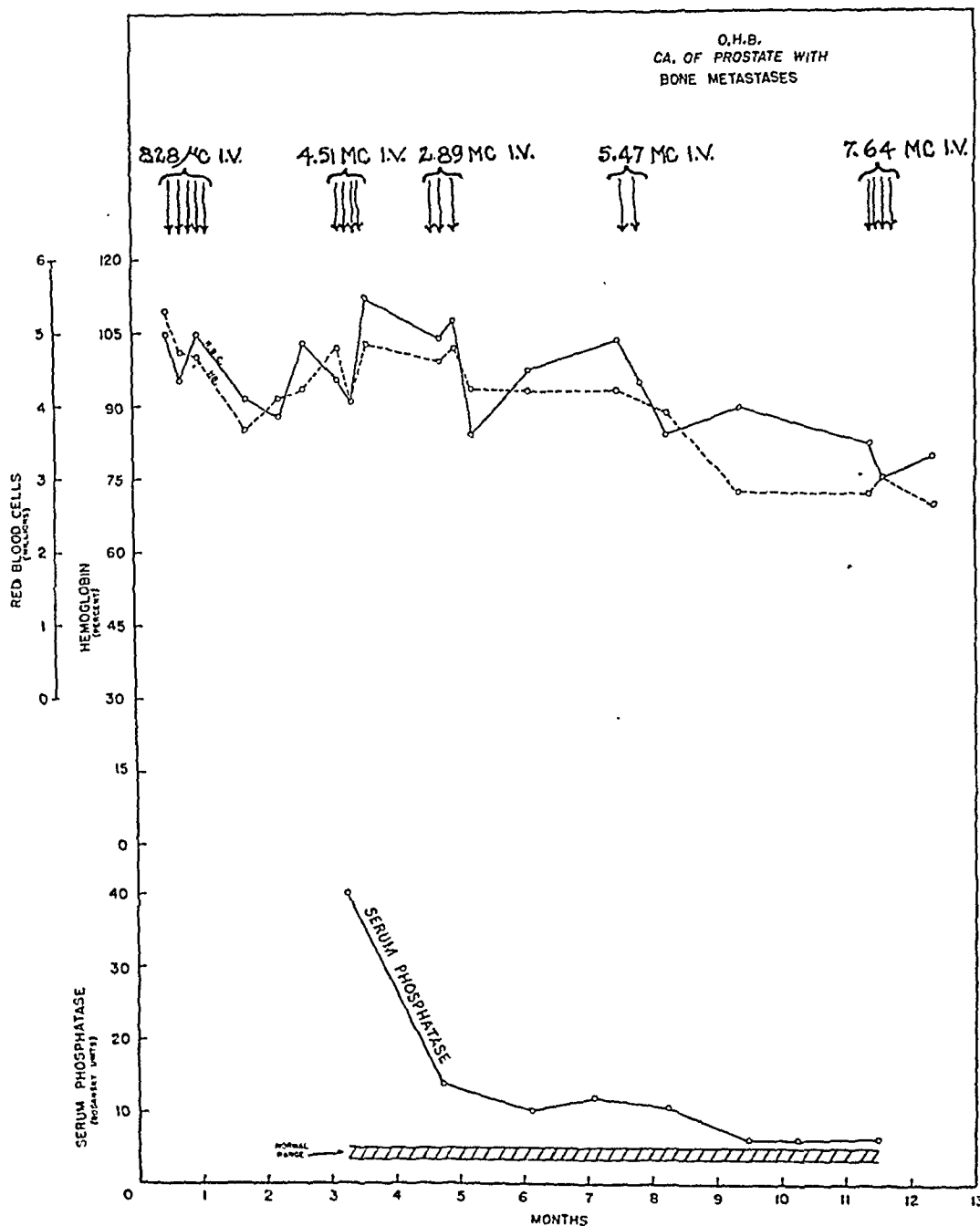


FIG. 1.—Carcinoma of the prostate with bone metastases: response of serum phosphatase, hemoglobin and red blood cell levels to radio-strontium therapy. (Arrows indicate fractioning of total doses shown.)

* Phosphatase activity was estimated by the method of Bodansky (*J. Biol. Chem.*, 99, 197, 1932; 101, 93, 1933) for the determination of alkaline serum phosphatase activity.

The recent work of Woodard and Higinbotham¹⁰ has demonstrated high phosphatase values in osteogenic tumors. In many such cases the phosphatase activity of the tissue is reflected in elevated values for serum phosphatase. These authors have also shown that inactivation of such tumors by external irradiation results in lowering the phosphatase activity of both the tumor and the serum. These facts, together with the demonstrated reduction of serum phosphatase activity by the administration of radio-strontium in the case cited above, suggested the possibility of a high uptake of strontium by osteogenic tumor tissue. The selective uptake of radio-phosphorus (P^{32}) in soft tissue tumor cells has been shown by Jones, Chaikoff and Lawrence² to be greater than in any other type of soft tissue. A parallel between this behavior and that of radio-strontium in osseous tumors would appear to be probable. Therefore, it has seemed desirable to investigate the metabolism of tumors of the bone with the aid of radio-strontium. Accordingly, small doses of radioactive strontium have been administered to 6 such cases, prior to biopsy or amputation, and the tissues have been assayed to determine uptake. The following is a report of these investigations.

Methods. 1. Radioactive strontium, first described by Stewart, Lawson and Cork,⁸ was prepared in the Berkeley 60 inch cyclotron by bombardment of metallic strontium with 16 million volt deuterons.

2. Tissues for assay were reduced to aliquots of approximately 1 gm. wet weight and ashed at 400° C.

3. Ashed samples were assayed for radioactivity on a standardized Du Bridge electrometer or a Geiger counter and compared with a uranium standard.

Results. CASE 1. W. L., 17-year-old white male school boy, weight 130 pounds, entered the University Hospital May 15, 1941, complaining of constant pain in the right hip. Past history revealed that the patient had fallen on his right hip 6 months earlier without immediate serious after-effects. In April the patient noticed that the right thigh was longer than the left and that he was limping. Swelling over the right femoral trochanter and upper portion of the right ilium had developed, and he had lost 15 pounds.

The family history shows that 1 brother died at the age of 7 years of osteogenic sarcoma following the fracture of the right femur. Another brother died at the age of 12 years of carcinoma of the colon.

The roentgenogram showed a large soft tissue mass with calcification arising in the right ilium and spicules radiating from it, the typical appearance of osteogenic sarcoma. A biopsy resulted in the diagnosis: chondrosarcoma (osteogenic sarcoma).

On May 20, 1941, 1462 μ c. of radio-strontium was administered intravenously, and on May 29 a second biopsy was taken.

The tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μ c./gm.	%/gm. tissue of dose
Muscle (normal?)	0.1475	0.010
Fat	0.00663	0.00045
Bone (apparently uninvolved)	0.244	0.0166
Bone and marrow	0.1948	0.0131
Bone (infiltrated)	0.498	0.034
Tumor	0.361	0.0246
Blood clot	0.0684	0.0046
Skin (normal)	0.342	0.0223

CASE 2. C. L., a 27-year-old white male, weight unknown, was admitted to the University Hospital in April, 1941. Past history showed that he had a spiral fracture of the right femur in 1937. One month later a roentgenogram of the knee joint revealed a tumor involving the external condyle. This was diagnosed radiologically as a giant cell tumor. No biopsy was made at that time.

The patient was treated with Roentgen ray, and the area became more dense and quiescent. In February, 1941, a tumor was noted involving the lower third of the thigh. Roentgen ray examination revealed a chiefly extracortical tumor showing elevation of the periosteum and small "specks of calcification within the tumor." On Roentgen ray films taken in April, 1941, the tumor still appeared to be extracortical. The old fracture line was still discernible. Radio-strontium (1183 $\mu\text{c.}$) was administered orally April 29, 1941, at 11 P.M. Amputation was performed April 30, 1941, at 12.30 P.M. Microscopic examination resulted in the diagnosis: osteoblastic osteogenic sarcoma of the femur.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, $\mu\text{c./gm.}$	%/gm. tissue of dose
Skin	0.0064	0.00054
Fat	0.00361	0.0003
Muscle	0.0036	0.0003
Femur	0.0131	0.0011
Marrow	0.0094	0.00079
Tumor	0.0073	0.00061

CASE 3. W. R., a 13-year-old white male student (weight 107 pounds), entered the University Hospital on June 24, 1941, because of gradual onset of pain and tenderness associated with pressure of a tumor mass in the upper right tibia region. Past history revealed that he was perfectly well until 7 weeks previously, at which time he was struck in this region by a soft baseball. The immediate pain subsided after a few days only to return about 1 week later and gradually to progress. The patient was then hospitalized. Temperature on entry was normal. There was a rather diffuse, egg-sized swelling over the antero-medial aspect of the upper end of the right tibia with some increased local temperature, moderate tenderness to pressure, and dilation of the superficial veins. There was no lymphadenopathy. Biopsy (June 26): osteogenic sarcoma. Radio-strontium (357 $\mu\text{c.}$) was administered intravenously July 2, 1941. Amputation was performed on July 7, 1941.

Figure 2 shows the roentgenogram and autoradiograph of the section submitted for activity assay.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, $\mu\text{c./gm.}$	%/gm. tissue of dose
Femur spongiosa	0.0066	0.0018
Femur epiphyseal line	0.106	0.029
Cartilage (femur epiphysis)	0.0318	0.0088
Bone with tumor (front)	0.1461	0.041
Bone with tumor (back)	0.1586	0.044
Muscle	0.0052	0.00146
Fat	0.0002	0.00005
Tumor	0.0996	0.0279
Skin	0.0772	0.0215
Femur cortex	0.0542	0.015

CASE 4. R. W., a 9-year-old white female (weight 85 pounds), was admitted to the University Hospital February 21, 1941. About 3 months prior to admission a small hard swelling was observed over the distal portion

of the ventral surface of the right forearm. This was not painful and did not appear to be inflamed. The motion of the wrist was not restricted. There was no history of trauma or injury. A Roentgen examination was made, and a diagnosis of bone tumor resulted. On a biopsy, the diagnosis of



FIG. 2.—*a*, Roentgenogram of section of leg (Case 3). *b*, Autoradiograph of section of leg (Case 3), showing concentration of Sr_{90} in tumor and at epiphyseal line.

Ewing's tumor of the radius was established. A series of Roentgen ray treatments was instituted immediately over the extremity and the chest, and the local mass disappeared almost completely. Roentgen examination, however, still revealed evidence of a tumor in the right forearm. Pain had developed during the 3 weeks prior to this examination. At the time of

admission there appeared to be no abnormality in the contour of the right forearm, by observation or palpation. There was no tenderness. About 9 months after the first admission the patient returned because of a rapidly increasing mass involving the right forearm. There was no tenderness except on very firm pressure. Roentgen examination revealed a definite increase in the tumor mass involving the right radius so that the entire shaft was then involved. There was extensive invasion of the soft tissues. No metastasis to the lungs was demonstrated. Radio-strontium (326 $\mu\text{c.}$) was administered intravenously September 25, 1941. Amputation was performed September 30, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, $\mu\text{c./gm.}$	%/gm. tissue of dose
Cortex of ulna (normal bone)	0.032	0.0098
Epiphyseal lateral humeral condyle (normal)	0.02442	0.007
Tumor, sample 1 (of radius)	0.0106	0.0032
Tumor, sample 2 (of radius)	0.0122	0.0033
Fat	Trace	
Muscle	Trace	
Skin	Trace	

CASE 5. O. E., a 54-year-old white male (weight 131 pounds), was admitted to the University Hospital August 22, 1941. About 18 months prior to admission the patient had developed pain in the posterior gluteal region over the sciatic notch. At the same time he developed a limp of the left leg. Six months later the pain had extended down to the inner aspect of the left knee. The left leg became weak and there was considerable muscle atrophy of the lower left extremity. During the 6 months preceding admission there was constant pain involving the left hip and the upper portion of the left thigh. There was moderate obstipation and 40 pounds loss in weight. On admission, examination revealed a large firm mass palpable in the lower left quadrant. There was considerable muscle atrophy of the left lower extremity. The motion of the extremity at the hip was limited in all directions. There was diminished pain to touch over the distribution of the left second and third lumbar segments with motor loss and atrophy of the abductors and of the flexors of the thigh. The left knee jerk was absent. Roentgen examination of the pelvis showed an extensive lesion of the bone involving the left ilium, ischium, and inferior pubic ramus. There was expansion of bone; moderate areas of bone destruction; periosteal thickening; and new bone formation. The appearance was strongly suggestive of osteogenic sarcoma. Radio-strontium (582 $\mu\text{c.}$) was administered intravenously September 3, 1941. A biopsy was performed September 9, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, $\mu\text{c./gm.}$	%/gm. tissue of dose
Bone tumor	0.483	0.082
Subcutaneous tissue and fascia (involved)	0.098	0.0016
Muscle	0.0124	0.0021
Skin	0.0086	0.0014
Fat	?	

CASE 6. C. B., a 21-year-old white male (weight unknown), was admitted to the University Hospital August 4, 1941. Seven months prior to admission the patient was struck by a heavy piece of metal which produced an ecchymotic area over the outer aspect of the right thigh and which seemed of no consequence. About 2 months later a slight swelling was observed. At the same time a pain developed in the region of the right thigh, but this was not severe enough to incapacitate him. One month prior to admission

the pain became more intense. An operation was performed and an encapsulated tumor was removed. This was diagnosed as myxo-fibro-osteosarcoma. Physical examination on admission revealed a firm, somewhat tender mass measuring approximately 10 cm. in diameter, directly above the incision resulting from the previous operation. On palpation the mass could not be clearly demarcated from the surrounding tissues. There was no evidence of inguinal metastasis. Roentgen examination revealed no metastasis to the parenchyma of the lungs, but examination of the upper

TABLE 1.—UPTAKE OF RADIO-STRONTIUM—MICROCURIES PER GM. AND % OF DOSE PER GM.—TISSUE—WET WEIGHT

	Case 1. W. L.	Case 2.* C. L.	Case 3. W. R.	Case 4. R. W.	Case 5. O. E.	Case 6. C. B.
Normal bone: $\mu\text{c./gm.}$	0.244	0.0131	0.0542	a. 0.0320 b. 0.0244	..	0.078
% dose/gm.	0.016	0.0011	0.015	a. 0.0098 b. 0.0070	..	0.012
Infiltrated bone: $\mu\text{c./gm.}$	0.0498	0.0073	a. 0.1461 b. 0.1586			
% dose/gm.	0.034	0.0006	a. 0.041 b. 0.044			
Tumor: $\mu\text{c./gm.}$	0.0361	..	0.0996	a. 0.0106 b. 0.0122	0.0483	0.588
% dose/gm.	0.0246	..	0.0279	a. 0.0032 b. 0.0033	0.082	0.090
Skin: $\mu\text{c./gm.}$	0.342	0.0064	0.0772	trace	0.0086	
% dose/gm.	0.022	0.0005	0.0215	..	0.0014	
Muscle: $\mu\text{c./gm.}$	0.1475	0.0036	0.0052	trace	0.0124	0.0005
% dose/gm.	0.010	0.0003	0.0014	..	0.0021	0.0007
Fat: $\mu\text{c./gm.}$	0.0066	0.0036	0.0002	trace	?	
% dose/gm.	0.0004	0.0003	0.0005			

* The short interval between administration of radio-strontium and amputation (12 hours) together with the fact that the radio-strontium was given orally probably accounts for the small uptake in all tissues.

right thigh showed a soft tumor mass in the upper portion of the thigh just below the trochanteric line. There was also an irregular area of calcification measuring approximately 6 by 3 cm. which was lateral and slightly posterior to the shaft of the femur. It appeared to have no connection with the femoral shaft. Radio-strontium (650 $\mu\text{c.}$) was administered intravenously August 2, 1941. An operation was performed August 6, 1941, and a tumor measuring 5 by 4 by 3 cm. was removed together with the surrounding muscle. There was no histologic evidence of malignant tumor in these tissues.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, $\mu\text{c./gm.}$	%/gm. tissue of dose
Bone (uninvolved)	0.078	0.012
Tumor	0.588	0.090
Muscle	0.005	0.0007

Discussion. Despite the marked difference in the uptake of radio-strontium by various tissues, there is ample evidence that the maximum occurs in bone and tumor tissues. In soft tissues variation is especially noticeable, but a somewhat striking concentration is observed in several of the cases in the skin. This has suggested the desirability of investigating the rôle of the skin in strontium metabolism. Such studies are now in progress in this laboratory. It is noteworthy that different parts of the tumor show marked differences in the uptake of strontium. This might be due (apart from causes such as vascularization, regressive local changes, and so on) to difference in the metabolic rate in different parts of the tumor.

depending on the state of cell development at the time of biopsy. The high uptake of strontium in areas where new bone is being laid down, whether this be normal or neoplastic, indicates that radioactive strontium will provide a valuable tool in the study of bone healing after experimental fractures. As with radioactive phosphorus in the case of new soft tissue cells, the rate of the laying down of new bone cells can be determined with labelled or radioactive strontium.

In order to evaluate the radiation effects of large doses of radio-strontium and to compare them with the effects of external sources of radiation such as Roentgen rays, it is desirable to attempt to convert the radiation emitted by radio-strontium into r units. This can be estimated from the energy of the emitted particles. Radio-strontium emits beta rays. Its half life is 55 days and its mean average life is 79.6 days. The maximum energy of radiation is 1.5 MEV. The particles from radioactive substances, however, have different energies (continuous spectrum); therefore, the mean energy values must be taken into calculations. For radio-strontium this is 0.75 MEV. According to this energy per particle: *One micro-curie of radio-strontium yields 38 r units daily per gram of tissue*, assuming uniform distribution. However, strontium is taken up mainly by osseous tissue, so that the radiation is concentrated chiefly in bones and osteogenic cells.

It would appear from the foregoing that indications exist for the experimental therapeutic use of radio-strontium in cases of certain bone tumors. Particularly this would appear to be justified in view of the exceedingly bad prognosis in such cases, and because of the meagre resources which now exist for their treatment. Because of the known high resistance of bone neoplasms to radiation, experience may prove that radio-strontium has therapeutic value chiefly as an adjunct to external radiation (Roentgen rays, radium, neutrons), as a means of increasing total radiation to the affected areas.

Pursuant to these ideas, radio-strontium is now being applied therapeutically in several of the cases here reported and in several patients suffering from skeletal prostatic metastases. Later publications will describe these clinical studies.

Summary and Conclusions. 1. Investigations concerning the metabolism of calcium and strontium by means of their inert and radioactive forms have been reviewed.

2. Preliminary clinical studies with radioactive strontium in breast and prostatic carcinoma with bone metastases are reported.

3. Administration of radioactive strontium to 6 cases of bone tumor prior to biopsy or amputation shows uptake chiefly by growing bone and by osteogenic tumor tissue.

4. Various considerations seem to justify the therapeutic use of radioactive strontium in certain bone tumors. Clinical studies along this line are now in progress and will be reported at a later date.

We wish to express our appreciation to the staff of the Radiation Laboratory, and particularly to Dr. Martin Kamen, for generous coöperation in supplying radioactive strontium used in this study. We are indebted to Dr. Joseph Hamilton for the autoradiograph shown in Figure 1, and we wish to thank Drs. Leroy Abbott, Keene Haldeman and other members of the Department of Orthopedic Surgery of the University of California Hospital for permitting us to carry on these studies on their patients.

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THE TOLERANCE OF RABBITS FOR THE AGGLUTINOGEN AND THE TOXINS OF *HEMOPHILUS PERTUSSIS**

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CONTROL of communicable disease requires either effective suppression of dissemination of the causal agent or adequate means of increasing the resistance of the population at risk. In the case of the air-borne diseases, measures directed toward controlling dissemination, such as ultraviolet irradiation and germicidal vapors, while promising, are still not operative on a scale significant to public health.

The practicability of increasing resistance to any disease is greatly influenced by the availability of (1) means of determining the distribution of susceptibility, and (2) an innocuous immunizing agent.

* This study has been supported in part by a grant from the United States Public Health Service. A grant has also been received from the Faculty Research Committee of the University of Pennsylvania. This is Paper IX of a series of studies with *H. pertussis*.

In the case of whooping cough there has been no suitable test for individual susceptibility, and the whole bacterial vaccine used to immunize is not entirely free from undesirable side reactions.

Work conducted at the University of Pennsylvania for a number of years has been directed toward preparation of suitable diagnostic and immunizing reagents from *Hemophilus pertussis*. An agglutino-gen has been prepared in a considerable degree of purity from *H. pertussis* of Phase I; this agglutino-gen is highly antigenic; when injected into the skin of non-immune animals or human beings, it has not caused reactions.^{6b} In the hands of Flosdorf, Felton, Bondi, and McGuinness⁵ this purified agglutino-gen has shown promise as (1) a test reagent for estimation of individual susceptibility, and (2) as a stimulating injection for increasing active immunity. The present study has elicited no evidence of this agglutino-gen being significantly toxic when administered intravenously to rabbits.

Physical disintegration of cells of *H. pertussis* by sonic vibration was used to insure that no possibly significant labile factors initially in the cells would be lost. By such delimiting means a stable agglutino-gen was found to be liberated. Although the agglutino-gen is stable, sonic extraction has been continued as the means of liberation of the agglutino-gen because of its convenience. Other components of the bacterial cell are also brought into solution in the sonic extract. One of these soluble components is a thermolabile toxin which has been shown to give a strong reaction of primary toxicity on injection into the skin of rabbits.^{4,6b} Storage of the pertussis cells or of their extracts or heating the extracts to 56° C. for 30 minutes destroys or alters the thermolabile toxin, leaving a less powerful thermostable toxin. Whether the thermolabile and thermostable toxins exist separately or in combination in the *H. pertussis* cell, or whether the thermostable toxin is an alteration product of the thermolabile component is not known. Both thermolabile and thermostable toxins are shown in the present study to cause pathologic changes on injection into rabbits.

Methods and Terminology. Washed cells of *H. pertussis* suspended in distilled water are disintegrated by the action of the sonic vibrator;⁷ the resultant material is centrifugalized. The opalescent supernatant fluid is called the *sonic extract*; it contains agglutino-gen, thermolabile toxin and thermostable toxin. Heating of the sonic extract for 30 minutes at 56° C. inactivates the thermolabile toxin, leaving thermostable toxin and agglutino-gen. This preparation is called *heated sonic extract*. The agglutino-gen has been purified from these toxins as previously described.^{6b} In text and in tables, injection of *agglutino-gen* implies this purified preparation.*

In the tables the amounts of materials injected are expressed both in milligrams of dry substance and in units of agglutino-gen contained in them. The purified agglutino-gen is assigned a unit value in terms of its capacity to combine agglutinin in quantitative absorption experiments;^{6a} 1 unit of

* In describing in detail the preparation and properties of these several materials in earlier publications,^{4,6b,8} the *sonic extract* was referred to as *SX-I*, the *heated sonic extract* as *heated SX-I*, the *purified agglutino-gen* as *A-I*, the *thermolabile toxin* as *TLT* and the *thermostable toxin* as *TST*.

TABLE 1.—THE LETHAL DOSE OF VARIOUS PREPARATIONS OF *H. pertussis* WITH THE CHANGE IN WEIGHT AND THE FORMATION OF AGGLUTININS FOLLOWING INTRAVENOUS INJECTIONS

Preparations	Dose			Number of animals			Change in weight (%)				Agglutinin titer
	Units of agglutinin*†	Total solids (mg.)‡	Number of doses	Used	Died	Survived	Last living		At autopsy		
							Range	Av.	Range	Av.	
Sonic extract	6	.25	2 to 5	3	3	0	-8 to -17	-14	±0 to -16	-8	120 to 160*
	3	.12	6 to 12	6	1	5	+1 to -18*	-4*	+8 to -21*	-4*	
	300	12.5	1	2	2	0	±0 to -10	-4	
	30	1.25	1	3	3	0	
Sauer's vaccine	6	.25	1	5	0	5	0 to trace** 20 to 80
	3	.12	1	2	0	2	
	50	2.5	3 to 4	2	2	0	-5 to -14	-9.5	-11 to -17	-14	
	25	1.3	6 to 12	4	1	3	±0 to -4*	-2*	±0 to -11*	-4*	
Sauer's vaccine	200	10.0	1	2	2	0	-8 to 13	-10.5	2,500 to 10,240*
	100	5.0	1	6	5	1	-11 to -22*	-16.5†	
	50	2.5	1	7	1	6	+3 to -13*	-3*	
	25	1.3	1	2	0	2	
Heated sonic extract	10	.5	1	2	0	2	-3 to -9	-6	160 to 2,560†† 2,500 to 5,120 640 to 2,560
	300	20.0	3 to 7	4	3	1	-9 to -11††	-10††	-4 to -19††	-11††	
	150	10.0	6 to 12	5	1	4	-5 to -14*	-10*	-3 to -21*	-12*	
	1,500	100.0	1	2	2	0	±0 to -5	-2.5	
Purified agglutinin	300	20.0	1	5	1	4	+4 to -5*	-2*	20§ trace to 1,280*
	150	10.0	1	5	1	4	
	2,000	6.0	3	2	0	2	+2 to -10	-4	+3 to -12	-4.5	
	1,000	3.0	6	2	0	2	+4 to -6	-1	-2 to -8	-5	
Purified agglutinin	200	.6	12	2	0	2	-4 to -9	-6.5	+2 to ±0	+1	80 to 160 1,280 to 2,560
	4,000	12.0	1	1	1§§	0	-1	
	3,500	10.5	1	1	0	1	-1	
	2,000	6.0	1	2	1§§	1	-1 to -10	-5.5	

* Only animals that survived.

** 3 out of 5 animals.

† 2 out of 5 animals that died.

†† 4 out of 6 animals that survived.

‡ Determined in salt-free solution (or suspension of organisms).

\$ Only animals that died.

§ 2 out of 4 animals that survived.

|| Death not due to infection, see text.

*† Estimated in case of Sauer's vaccine on basis of extractable agglutinin; 1 ml. containing 10¹⁰ organisms is equivalent to 10 units of agglutinin.

the purified agglutinin solution usually contains 0.001 or 0.002 mg. of total solids. The purpose of listing the units of agglutinin in the sonic extracts is to afford a comparison of the toxicity of the thermolabile and thermostable toxins contained in these extracts in relation to the content of agglutinin.

Chinchilla rabbits weighing about 2 kg. were injected with single doses or with repeated daily doses of various quantities of purified agglutinin or of sonic extract or heated sonic extract. Animals which were sacrificed were killed by ether. Pieces of heart, spleen, liver, brain, lungs, kidneys, adrenals, and popliteal lymph nodes were fixed in formalin. The sections were stained with hematoxylin-eosin, and sections of the liver were stained for fat, and sections of the spleen for iron.

TABLE 2.—LETHAL DOSES OF VARIOUS FRACTIONS OF *H. PERTUSSIS* EXPRESSED IN UNITS OF AGGLUTININ

	Single injections	Repeated daily injections
Sonic extract	6-30*	3-6
Sauer's vaccine	50-100	25-50
Heated sonic extract	300-1500	150-300
Purified agglutinin	>3500	>2000

* The boldface data are closer to the exact lethal doses than those not boldface.

Results. Some results of the study are presented in Table 1. They include the lethal doses, the changes in the weight of the animals, and the agglutinin titers. In order to facilitate the interpretation of the data, summaries of certain findings and the results of some calculations are presented in subsequent tables.

Lethal Doses. From the data in Tables 1 and 2, it will be observed that the range of lethal doses varies from, in the case of the sonic extract, a quantity containing 6 to 30 units of agglutinin up to a quantity of purified agglutinin representing 3500 units of agglutinin injected as a single dose. In the case of repeated daily doses, the lethal range varied from 3 to 6 units in the case of sonic extract to more than 2000 units of purified agglutinin. It is true that Rabbit 270 died after 2000 units of purified agglutinin, and Rabbit 275 after 4000 units. However, both these experiments were performed during the last days of July, 1941, when the animals suffered greatly from heat. Moreover, other rabbits receiving 3500 units, or repeated doses of 2000 units, not only survived, but also showed no change in blood picture and no tissue reaction.

Changes in Weight. All animals that succumbed to injection of the sonic extracts lost considerable weight (Table 1). If they died 1 to 2 days after the first injection, they were found to have lost an average of 9%, while after 6 to 7 injections this loss amounted to 25%. The animals which survived, on the other hand, showed little if any change in weight. As a matter of fact, only 1 of these animals was found to lose more than 6% during the first day following a single injection, and only 1 lost more than 9% during the first 6 days of repeated daily injections, the average weight loss amounting to as little as 3% in the former group, and 4% in the latter.

TABLE 3.—ERYTHROCYTE AND LEUKOCYTE CHANGES AFTER SUBLETHAL DOSES OF VARIOUS PREPARATIONS OF H. PERTUSSIS

Preparations	Dose		Number of erythrocytes (millions)			Hemoglobin (%)			Number of leukocytes (thousands)			Number of granulocytes (thousands)			Number of lymphocytes (thousands)		
			No. of rabbits			Days after injection			Control			Days after injection			Control		
	Atrolinogen, Total solids (mg.)	Repeated, times															
Sonic extract	6	0.25	332	331	331	6.0	5.0	6.3	77	78	74	80	74	82	77	78	74
Sonic extract	3	0.12	338	337	337	6.0	5.0	5.8	63	81	79	71	70	77	78	74	82
Sonic extract	3	0.12	360	367	367	5.7	4.8	5.3	78	80	70	71	70	77	78	74	82
Sonic extract	50	2.5	360	365	365	6.3	4.8	5.3	70	83	75	82	70	77	78	74	82
Sonic extract	25	1.3	362	361	361	5.2	4.5	5.0	68	70	75	82	70	77	78	74	82
Sonic extract	25	1.3	370	369	369	4.8	5.1	5.5	81	74	76	80	70	77	78	74	82
Sonic extract	10	0.5	375	376	376	6.6	4.3	5.3	74	71	88	78	70	77	78	74	82
Sonic extract	300	20.0	351	350	350	5.7	5.0	5.0	77	72	70	70	70	77	78	74	82
Sonic extract	150	10.0	360	359	359	5.2	4.3	5.3	62	66	65	64	63	65	67	64	67
Sonic extract	150	10.0	368	373	372	5.1	5.0	5.5	62	64	63	65	67	64	67	64	67
Sonic extract	3500	10.5	371	370	370	5.0	4.5	5.0	81	79	84	75	85	75	85	75	85
Sonic extract	2000	6.0	374	373	373	5.0	4.5	5.0	80	80	70	71	70	77	78	74	82
Sonic extract	2000	6.0	361	360	360	5.3	4.8	5.3	72	78	70	67	71	77	78	74	82
Sonic extract	1000	3.0	289	288	288	5.0	4.3	5.7	83	83	73	75	73	77	78	74	82

* In animals that received repeated injections these columns refer to 3, 7 and 10 days after the first injection.

† Rabbit 288 suffered from an acute relapsing infection of the omentum.

Changes in the Blood. The behavior of the red and white blood cells was studied in 26 rabbits which received sublethal doses of the several preparations (Table 3). A slight drop in the number of erythrocytes and hemoglobin percentage was observed in all animals which received the highest sublethal doses; those which received lower doses did not show this change. A leukocytosis was found after single doses of sonic extract containing 6 units of agglutinin, of Sauer's vaccine containing 10 to 50 units, and of heated sonic extract containing 150 to 300 units, as well as after repeated doses of Sauer's vaccine containing 25 units and sonic filtrate containing 30 units. The lymphocytes rose highest after Sauer's vaccine, and remained low in most cases injected with heated sonic extract. The granulocytes rose highest after injection of heated sonic extract and remained low after injection of sonic extract. In other words, after injection of sonic extract the leukocytosis was almost exclusively a lymphocytosis, and with Sauer's vaccine a lymphocytosis and granulocytosis, while after injection of heated sonic extract it was, in most cases, predominantly a granulocytosis. After injection of purified agglutinin no leukocytosis was observed.

Organ and Tissue Changes. If we turn now to the individual organs and tissues and first consider the *weights of the organs* where these were taken (Table 4), it may be observed that lungs, spleen and kidneys showed a considerable rise in weight, and liver and heart a moderate increase, in all animals that succumbed to injections; while the animals which survived showed no distinct change in weight except in the spleen, the weights of which were double or almost double the normal weights in the rabbits which received Sauer's vaccine or heated sonic filtrate. These differences were apparent not only in the absolute weights of the organs, but also in the relative weights, *i. e.*, grams per kilo of body weight, whether these were calculated from the initial weights of the rabbits before they were injected (relative weights I), or from the final weights determined at the time of death (relative weights II) (Table 4).

TABLE 4.—CHANGES IN WEIGHT OF ORGANS EXPRESSED IN PER CENT OF NORMAL*

	<i>After Lethal Doses.</i>				
	Lung	Spleen	Kidneys	Liver	Heart
Absolute weights	+80	+50	+54	+11	+11
Relative weights I	+86	+60	+59	+14	+13
Relative weights II	+105	+80	+78	+29	+26
<i>After Sublethal Doses.</i>					
Absolute weights	+12	+40	+11	+2	+2
Relative weights I	+5	+40	+6	+4	-4
Relative weights II	+10	+40	+11	+7	±0

* Changes in absolute weights were calculated by comparing organ weights of sacrificed rabbits with those of normal rabbits. Relative weights refer to weights of organs per kilo of body weight; I refers to those compared with body weights at beginning of the experiment; II refers to those at the end, *i. e.*, after weight loss had occurred.

While the increase in weight of the kidneys, the liver and the heart was chiefly due to cloudy swelling, the increase in weight of the spleens after lethal doses was mainly caused by hyperemia, and that of the lungs by both hyperemia and edema. Differences in weight as produced by the various fractions of *H. pertussis* were not discovered; however, the average weight increase was greater in animals which died after repeated injections than in those which succumbed to the first dose.

The most conspicuous *tissue changes which were observed after lethal doses* were necrosis in liver, adrenals and kidneys, as well as in the lymphatic tissue of spleen and popliteal lymph nodes (the only lymph node studied). In the liver, necrosis was present in all animals which succumbed to injections except in Rabbit 249 which died (as late as) 7 days after a single injection of Sauer's vaccine, and in the 2 rabbits which died during a heat spell following a large single injection of purified agglutinin (Rabbits 270 and 275). In the adrenals necrosis was observed only in 4 out of 13 animals which died and whose adrenals were studied microscopically, and in the kidneys only in 3 animals. In the liver of 2 rabbits (242 and 243) and in the kidneys of 1 rabbit (360) the necrotic tissue was found to be calcified. This seems to indicate that at least in these rabbits the necrosis was produced by the first or one of the first of the repeated daily injections of the fractions used.

In the spleens, too, necrosis was present in almost all animals. In some we found merely increased nuclear decay in the Malpighian bodies; in others focal necrosis was observed in both the follicles and the lymph sheaths; while in most we found extensive necrosis throughout the white pulp. The red pulp was mostly observed to be hyperemic, and often contained large plasma drops and swollen macrophages. In animals which succumbed after repeated injections the structure of the spleen appeared to be markedly loosened, and the white pulp was much reduced in quantity.

In the popliteal lymph nodes the necrosis was not as conspicuous as in liver and spleen. Of 15 rabbits which succumbed to injections and the lymph nodes of which were studied microscopically, only 2 showed extensive necrosis with diffuse hemorrhages throughout the parenchyma, while 11 showed all transitions from increased numbers of pycnotic nuclei in the secondary nodules to marked necrosis of the cortex. In most animals, the nodes were markedly hyperemic, and the central sinuses were sometimes distended with lymph.

Among the animals which survived, on the other hand, necrosis in liver and adrenals was found only in Rabbit 232 which was killed 1 day after the highest single sublethal dose of heated sonic filtrate. It may very well be that this rabbit would have died spontaneously if it had not been sacrificed so shortly after the injection.

The most conspicuous *tissue changes of the animals which survived*

were hyperplasia of the lymphatic tissue particularly in the spleen, and foci of extramedullary myelopoiesis in spleen and liver. Lymphatic hyperplasia in the spleen with large so-called germinal centers was observed especially after single injections of Sauer's vaccine containing 50 to 100 units of agglutinin or repeated injections containing 25 units; it was present in some and absent in other animals which received heated sonic filtrate or purified agglutinin. After single or repeated injections of sonic filtrate containing 3 to 6 units of agglutinin, the secondary nodules as well as the lymph sheaths remained undisturbed. A mild lymphocytic hyperplasia was observed also in the popliteal lymph nodes of the animals which were injected with Sauer's vaccine, but it was absent after heated sonic filtrate.

Foci of extramedullary myelopoiesis were most marked and regularly present in both spleen and liver, in all animals which survived repeated injections of sonic filtrate, Sauer's vaccine, and heated sonic filtrate. After single injections of these fractions, such foci were observed in 8 spleens and 5 livers among 16 animals, while after injections of purified agglutinin they were found only in the spleens of 3 out of 8 animals. The latter, to be sure, may have been due to causes other than the injections.

As to *other tissue changes* which were observed in our rabbits, those in lungs and brain deserve mentioning. Foci of chronic interstitial or bronchial pneumonia were detected in 27 out of 60 experimental animals, and foci of encephalitis were found in 6 out of 39 experimental animals. Since both these lesions were equally common in all our experimental groups as well as in our control animals, their occurrence is regarded as coincidental.

Mesenchymal reactions in the vascular connective tissue of lungs, liver and spleen as observed after intravenous injections of large doses of killed staphylococci, streptococci or colon bacilli^{2,3} were seen only in 6 experimental and 1 control animal and seemed to be entirely independent of the treatment which they received.

Finally, it should be mentioned that the fat and iron metabolism as apparent in liver and spleen from fat and iron stains were not significantly altered in the experimental animals. The amount of fat which was found in the liver varied greatly in the different experimental groups and individual animals; and the amount of iron that could be demonstrated in the spleen likewise varied considerably; though it was found to be higher in animals which survived than in those which died, and seemed to be higher in those which survived repeated injections. However, in no experimental group was the amount of iron to be found greater than in our control animals.

Discussion. The various fractions of *H. pertussis* which have been studied differed not only in their toxicity, but also in their rôle in the production of certain pathologic changes. Expressed by weight of total solids, unheated sonic extract was 80 times as toxic as heated sonic extract.

While the lethal effect of sonic extract was obviously principally due to the thermolabile toxin, that of the heated sonic extract, like that of Sauer's vaccine, was probably due to the thermostable toxin; the effect of purified agglutininogen cannot yet be analyzed because no dose large enough to be lethal could be given to establish it. As to the mechanism of the death after lethal doses, it appears that this was the same with all the preparations, because the animals which succumbed to injections all showed the same histologic changes,* namely congestion and edema of the lungs; cloudy swelling of kidneys, liver and heart; and necrosis especially of liver and the lymphatic tissue of the spleen. Though it may be that shock was a factor concerned, the necrosis of the lymphatic tissue, together with the well-known lymphocytotic effect of *H. pertussis* in man suggest a more specific mechanism.

The pathologic changes which are observed in blood and tissues in pertussis or in bronchitis as observed in human patients have not been seen in our animals. Lymphocytosis and granulocytosis, on the other hand, were regularly present after certain doses; and a mild anemia was observed after high sublethal doses; and there was hyperplasia of the lymphatic tissue especially of the spleen, and extramedullary myelopoiesis in liver and spleen.

As to the nature of the factors that caused these reactions, the data of Table 3 first seemed to confirm the conclusion of Camerer¹ that the lymphocytosis was caused by the thermolabile toxin. However, like Fukushima⁹ and Tuta,¹¹ we saw lymphocytosis also in some animals which received heated extract, and a certain parallelism seemed to exist between lymphocytosis, agglutininogen units and agglutinin titers. The latter observation is of interest in the light of Takahashi's claim according to which the lymphocytosis produced by *H. pertussis* can be neutralized by the injection of pertussis immune serum.¹⁰

As to the reaction of the granulocytes in our experiments, it was noted that a granulocytosis was present after injection of heated sonic extract containing 150 units of agglutininogen but absent after 3500 units of purified agglutininogen, though in both these cases the total solids amounted to about 10 mg. each. This observation could be interpreted to indicate that the granulocytosis was not merely a function of the protein contained in the preparations, but was caused probably by the thermostable toxin.

If, finally, we attempt to determine the greatest non-toxic doses of the various fractions, much depends on whether we look upon granulocytosis and lymphocytosis observed in these animals as harmful or beneficial. If we regard them as beneficial, the greatest non-toxic doses of the fractions would lie close to the lower of the 2 lethal doses as given in Table 2; while if we regard them as harmful

* A few rabbits were injected with lethal doses of living organisms and the histologic changes which were observed in these were the same as those produced by sonic extract.

the greatest single non-toxic dose of sonic extract would contain 3 units of agglutinin, that of heated sonic extract somewhat less than 150 units, and that of the purified agglutinin more than 3500 units. In the latter case, according to this calculation, the purified agglutinin would be less than one one-thousandth as toxic as the sonic extract of the whole virulent organisms.

Summary. The relative toxicity of certain fractions of *H. pertussis* as well as their rôles in the production of certain pathologic changes in blood and tissues have been studied experimentally in rabbits. The agglutinin is important in establishment of anti-bacterial immunity and the purified agglutinin is giving promise as a reagent for use in intradermal testing for susceptibility to whooping cough. The purified agglutinin contains neither thermolabile nor thermostable toxin. No evidence of toxicity of the purified agglutinin was found when tested in dosage 300 to 1000 times greater than the lethal dosage of the thermolabile toxin. Thus, there is a wide margin of safety in the clinical application of the purified agglutinin.

In the blood, a mild transient anemia was observed after high sublethal doses, and a leukocytosis also after lower doses, of preparations containing one or both toxins. With sonic extract the leukocytosis was almost exclusively a lymphocytosis; with Sauer's vaccine both a lymphocytosis and granulocytosis; and with heated sonic extract in most cases predominantly a granulocytosis. The two leukocytoses, therefore, appear to be caused by different toxins of *H. pertussis*. It may well be that the thermostable toxin does not exist natively as such, but is in complex combination with the thermolabile toxin; the thermostable toxin may appear only as a result of the reaction by which the thermolabile toxin becomes inactivated. No leukocytosis was found after massive doses of purified agglutinin.

The tissue changes after lethal doses of the toxins included congestion and edema of the lungs, cloudy swelling of kidneys, liver and heart, and necrosis especially in liver and lymphatic tissue of the spleen. In surviving animals there were lymphatic hyperplasia especially in the spleen, and extramedullary myelopoiesis in liver and spleen.

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THE EFFECT OF ACID AND ALKALINE SALTS ON SOME PATIENTS WITH RHEUMATOID ARTHRITIS

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Low grade edema, which is frequently part of the clinical picture presented by arthritic patients, is often ignored, and its rôle in the disease is not clearly understood. Scull and Pemberton⁶ have called attention to this edema or "tissue swelling" and have observed that, with bed rest and a low carbohydrate diet, arthritic patients often experience relief of pain, decrease in joint swelling, and an increase in joint mobility concomitantly with the loss of water from the body.

It has also been demonstrated^{4,5} that synovial fluid may be regarded as a dialysate of plasma containing mucin, and that the presence of edema from any cause may be associated with an increase in the volume of synovial fluid.² These observations suggest that the volume of synovial fluid of arthritic patients may be related to the volume of the extracellular fluid compartment of the body.

In this study the clinical effects of water loss occurring after diuresis by ammonium chloride, and the clinical effects of water retention resulting from the administration of sodium bicarbonate were observed in 5 patients with rheumatoid arthritis.

Procedure. Five female patients with chronic rheumatoid arthritis were studied. They were placed on a diet containing 150 gm. carbohydrate and 75 gm. protein. The caloric value of the diet was adjusted for each patient by adding sufficient fat so that 40% more than the basal caloric requirement as estimated from the tables of Dubois and modified by Boothby and Sandiford¹ was given. The diet was the same every day for each patient and prepared so that it contained less than 2.5 gm. sodium chloride. Water was unrestricted, although the daily water intake was estimated and the urinary output was measured. The patients were weighed daily on a balance accurate to 1 gm. Under these circumstances it can be assumed that changes in body weight reflect water loss or water retention.³ All patients had been hospitalized for several weeks or months prior to the experiments, and the symptoms resulting from the arthritis remained unimproved. None had menopausal symptoms. The patients received no physiotherapy, and analgesics were administered upon request of the patient during the course of these experiments.

* Supported by a grant from the Upjohn Company.

The patients were examined every morning. The mobility of the affected joints was measured and expressed in terms of degrees of range of motion (the degree of maximum extension minus the degree of maximum flexion) the circumference of the joints was measured. The symptom of pain was evaluated by careful questioning of the patient and noting the frequency with which she requested analgesics.

After control joint measurements were made over a period of 3 to 5 days the patients were given 6 to 8 gm. ammonium chloride daily for varying lengths of time. The ammonium chloride period was followed by the administration of 6 to 8 gm. of sodium bicarbonate for 7 to 10 days, and the same observations were made. The experiment was concluded by repeating the administration of ammonium chloride.

Results. Table 1 shows the detailed data on Patient 1. The remaining 4 patients responded similarly and their summarized data are shown in Table 2. Although there were individual variations in clinical response to the administration of ammonium chloride and sodium bicarbonate, the character of the response was remarkably similar in each case.

TABLE 1.—DATA ON PATIENT B. R.*

Date, 1940	Period	Weight in (kg.)	Range of motion (degrees)			Circumference (cm.)		Pain
			Right knee	Left knee	Left elbow	Right knee	Left knee	
10-16	Control	48.3	30	40	64	36.4	32.5	++
10-19	"	48.0	30	40	63	36.5	32.5	++
10-20	NH ₄ Cl	47.9	30	40	65	36.5	32.5	++
10-22	"	46.3	40	45	70	35.4	31.0	+
10-24	"	45.4	55	55	70	34.0	31.2	0
10-26	"	44.3	70	60	85	33.0	31.5	0
10-30	"	41.8	85	85	112	32.0	31.5	0
11-3	NaHCO ₃	41.9	84	90	110	31.4	31.2	0
11-5	"	42.8	70	70	105	33.0	33.0	++
11-8	"	45.2	64	65	50	35.0	35.0	+++
11-11	NH ₄ Cl	46.0	50	50	35	35.0	35.5	+++
11-13	"	44.5	60	70	50	34.5	35.0	++
11-16	"	42.0	80	65	65	33.5	33.5	0
11-22	"	40.8	86	85	70	34.0	32.5	0
11-30	"	42.0	80	82	70	34.0	33.0	0
12-8	"	41.0	80	80	70	34.0	33.0	0
12-9	NaHCO ₃	41.7	80	80	75	34.0	33.0	0
12-11	"	43.0	50	70	70	34.0	34.5	+++
12-15	"	45.4	45	40	50	35.5	35.5	+++
12-16	NH ₄ Cl	46.2	40	42	50	35.5	35.5	+++
12-18	"	45.4	55	70	60	35.0	34.0	+
12-22	"	41.7	100	95	75	33.0	33.0	0

* Every other set of determinations has been omitted by editorial request, in order to save space.

In each case the period of ammonium chloride administration was characterized by a significant decrease in body weight which under the conditions of the experiment can be assumed to be mainly due to water loss from the body.³ Associated with the water

loss there was a decrease in joint swelling as measured by the joint circumferences. In Cases 1, 2, and 3 there was also a progressive increase in the mobility of the joints. Cases 4 and 5 showed no significant change in mobility but Case 4 had relatively little impairment of joint mobility initially, and Case 5 had very severe joint destruction with some ankylosis. All patients experienced relief of joint pains during the period of ammonium chloride administration. Relief of pain occurred even though the range of motion was not significantly altered (Patient 5).

TABLE 2.—DATA ON 4 PATIENTS

	Control period, 3-5 days	NH ₄ Cl period, 23-33 days	NaHCO ₃ period, 7-10 days	NH ₄ Cl period, 6-8 days
Patient (A. B.):				
Weight (kg.)	80.0	74.2	78.6	75.5
Right shoulder:				
Abduction (deg.)	30	80	65	90
Extension (deg.)	30	100	60	120
Right knee—circumference (cm.)	41.5	39.0	41.0	39.0
Left knee—circumference (cm.)	40.0	40.0	41.0	39.0
Pain	+++	0	+++	0
Patient (V. B.):				
Weight (kg.)	31.2	27.7	30.9	28.6
Right shoulder—abduction (deg.)	60	90	45	90
Right knee—range of motion (deg.)	80	155	112	150
Right knee—circumference (cm.)	29.5	28.0	31.0	29.5
Left knee—range of motion (deg.)	0	65	65	90
Left knee—circumference (cm.)	29.0	25.0	29.0	25.5
Pain	+++	0	+++	0
Patient (I. S.):				
Weight (kg.)	53.2	51.0	54.0	51.7
Right knee—circumference (cm.)	35.0	33.0	35.0	33.0
Left knee—circumference (cm.)	35.5	32.0	34.0	31.0
Right ankle—circumference (cm.)	26.5	23.0	25.0	25.0
Left ankle—circumference (cm.)	26.5	24.0	27.0	25.0
Pain	0	0	+++	0
Patient (A. K.):				
Weight (kg.)	59.3	57.9	59.1	57.1
Right shoulder—extension (deg.)	135	170	135	150
Right knee—circumference (cm.)	37.0	34.5	37.0	35.0
Left knee—circumference (cm.)	36.5	34.0	36.0	34.0
Right ankle—circumference (cm.)	30.0	25.0	30.0	29.0
Left ankle—circumference (cm.)	29.0	26.0	28.0	26.0
Pain	++	0	+++	0

The period of sodium bicarbonate administration was characterized by an increase in body weight and in joint swelling. Joint mobility was significantly decreased and in some instances joints essentially asymptomatic before the onset of these observations became swollen and painful. Pain was aggravated in each case. Case 4, who had had no pain initially, developed severe pains. Case 5 developed more pain while receiving sodium bicarbonate than she had initially.

Discussion. Under the conditions of these experiments, the changes in body weight which were observed can be assumed to

represent mainly either water retention or water loss.³ It was to be expected, therefore, that the period of ammonium chloride administration should be characterized by a reduction in body weight due to water loss, since the diuretic effect of ammonium chloride has been demonstrated by numerous investigators. Similarly, an increase in body weight following the administration of sodium bicarbonate must be attributed to an increase in the water content of the body. In these cases of rheumatoid arthritis the decrease in body weight and in joint circumference with the administration of ammonium chloride, and the increase in body weight and joint circumference with sodium bicarbonate suggests that the fluid in the joints and in the periarticular tissues, as well as the extracellular fluid volume, is affected by these drugs.

The results of these observations are in general agreement with the observation of Scull and Pemberton⁶ that the loss of body water in rheumatoid arthritis is associated with clinical improvement. This would suggest that in rheumatoid arthritis the symptom of joint pain is caused, at least in part, by the swelling of articular and periarticular tissues. Similarly, in the absence of definite bony ankylosis, the immobility of the joints in rheumatoid arthritis may be partly due to this swelling and the pain resulting therefrom. To the extent that this is true, and in the absence of definite joint ankylosis, the reduction of tissue edema may be expected to be associated with clinical improvement of the patient as manifested by relief of pain, decrease in the swelling of the affected joints, and an increase in their range of motion. The fact that these changes are readily reversed with the administration of sodium bicarbonate supports such a view.

Other patients not as carefully studied, and not included in this report, have been tried on this régime and similar changes were not uniformly observed. The response was judged largely on the basis of subjective changes and was not as impressive. Some patients noted no changes at all, some rather insignificant improvement with ammonium chloride, and others were moderately benefited. Sodium bicarbonate administration was more often associated with an increase in the severity of symptoms.

It is not the purpose of this report to recommend ammonium chloride or other diuretics as a therapeutic measure in rheumatoid arthritis. However, the striking clinical changes observed in this small series of patients with alterations in the body water suggest the need of further investigation of the rôle of water in this disease.

Case Reports. CASE 1. B. R., a 44-year-old white female, had had rheumatoid arthritis for 10 years. At the time these observations were made she was bedridden because of multiple joint involvement. There was pain on motion of both shoulder joints, pains in both elbows and limitation of motion of the left elbow. Both wrists were painful and swollen. The hands showed interosseous atrophy and fusiform swelling about the metacarpo-phalangeal and the proximal phalangeal joints. There was

extreme pain on motion of the hip joints, more marked on the right. Both knee joints were swollen, painful, and limited in motion. The right ankle was swollen, painful, and limited in its range of motion. Although many of the joints were swollen, there was no evidence of pitting edema.

Roentgen ray revealed slight loss of joint space in both knees with decalcification of the adjacent bone. The other joints showed marked decalcification of the adjacent bones, some loss of joint space, but no ankylosis.

After control joint measurements were made for 4 days, the patient was given 8 gm. ammonium chloride daily for 13 days (Table 1). Her weight decreased 6 kg. Concomitantly with the decrease in weight there occurred a significant increase in range of motion of the right knee, left knee, left elbow and both hips. The circumference of the right knee decreased significantly. The circumference of the left knee was also decreased, although not to such a marked degree. All joint pains were remarkably relieved. There was a decrease in the swelling of the left wrist and an increase in the mobility of this joint. The patient tolerated the ammonium chloride well, and she felt generally improved.

Following the period of ammonium chloride, the patient was given 8 gm. sodium bicarbonate daily for 8 days. The changes in measurements are shown in Table 1. During this time her weight increased 4.1 kg. There was a complete reversal of the changes noted in the preceding period. The circumference of the left knee which had not changed remarkably under the influence of ammonium chloride now increased significantly. Joint pains which had been relieved by ammonium chloride became severe, the patient complained bitterly and required analgesics.

The alternating periods of ammonium chloride and sodium bicarbonate were repeated. Each time the periods of sodium bicarbonate administration were characterized by an increase in body weight, increase in joint circumferences, decrease in joint mobility, and increase in joint pain. On the other hand, the periods of ammonium chloride administration were characterized by a decrease in body weight, decrease in joint circumference, increase in joint mobility, and relief from joint pains.

CASE 2. A. B. was a 38-year-old white female whose arthritis was of 1 year's duration. At the time these observations were made she exhibited limited ability to abduct or extend the right shoulder. There was swelling of both knees and both ankles, and although their mobility was not impaired to passive movement, she was unable to walk because of pain and limitation of active motion. The patient required 45 gr. of acetylsalicylic acid daily to control her pain, and she was given codein every night to assure a night's sleep. Roentgen rays of the affected joints revealed no ankylosis and no joint destruction.

The patient was given 8 gm. ammonium chloride daily for 22 days. During this time her weight decreased 5.8 kg. The degree of abduction and extension of the right shoulder were significantly increased. Swelling of the right knee and ankles decreased. Joint pains which had been a prominent symptom previously were completely relieved, analgesics were unnecessary and she was able to walk.

Ammonium chloride was then discontinued and 8 gm. sodium bicarbonate were administered daily for 15 days. The patient's weight increased. The swelling of the knees and ankles returned. Pain promptly reappeared and became even more severe.

The final period of ammonium chloride administration (8 days) was again characterized by a loss of weight, increased mobility of the shoulder, and diminished circumference of both knees. Joint pains were again completely relieved. This patient was sufficiently improved to be discharged to the outpatient department. Table 2 shows the summarized data on this patient.

CASE 3. V. B. was a 28-year-old white female whose illness was of 3 years' duration. At the time of these observations the patient complained of severe pain and stiffness of the cervical, dorsal, and lumbar spine. There was pain and limited abduction of the right shoulder; pain, swelling, and limited motion of the right knee and both ankles; pain, swelling, and fixation at an angle of 90° of the left knee. Roentgen ray examination showed no evidence of bone or joint changes in the cervical, dorsal, or lumbar spine. There was decalcification of the bones of both knees and ankles with sharply etched articular surfaces but no ankylosis.

The patient was given 6 gm. ammonium chloride daily for 26 days. During this time her weight gradually decreased 3.5 kg. The degree of abduction of the right shoulder increased significantly. The range of motion of both knees and ankles increased while the swelling decreased. Pain was remarkably relieved and no medication was needed. Mobility of the spine was not affected although back pain was relieved.

Following this period, 6 gm. sodium bicarbonate were administered daily. As is indicated in Table 2, the patient gained approximately 3.2 kg. in weight. Pain of the joints became a very prominent symptom so that she required codein. The swelling of the joints increased and, in general, the range of motion decreased.

In the final period of ammonium chloride administration the symptoms of pain again disappeared completely. Swelling of the joints decreased. The range of motion of the knees and right shoulder was further increased, and the patient felt considerably better.

CASE 4. I. S. was a 48-year-old white female whose rheumatoid arthritis had become progressively worse over a 10-year period. At the time these observations were made, there was swelling of the dorsal surfaces of both hands and of both knees, although mobility was not markedly impaired. Both ankles were swollen and moved with difficulty. Pain of the joints was not a prominent symptom at this time. Roentgen ray revealed marked narrowing of joint spaces in the left hand and knees.

During a 23-day period of ammonium chloride administration the patient's weight decreased 3.2 kg. The circumferences of the knees and ankles decreased significantly, the puffiness of the dorsal surfaces of the hands disappeared and the mobility of the fingers improved.

During the next 10 days the patient received 8 gm. sodium bicarbonate daily and gained 3 kg. in body weight. The circumference of the affected joints increased to approximately their initial size. Joint pain, which had previously not been a prominent symptom, became severe and the patient required codein for its relief. Swelling of the dorsal surfaces of the hands reappeared and the patient complained of numbness of the fingers of both hands.

During the final period the patient received 8 gm. ammonium chloride daily for 7 days. The weight again decreased. The circumferences of the knees and ankles diminished, and joint pain was relieved.

CASE 5. A. K., a 47-year-old white female, had had rheumatoid arthritis for 8 years. When these studies were begun, she complained of pain and restriction of motion of both shoulder joints, more marked on the right. Both elbows, wrists and knees were swollen, painful and limited in motion. The ankles and toes were deformed and not movable. Analgesics were continually required.

Roentgen ray revealed destruction of many of the joint spaces with bone erosion and decalcification of all the bones.

For 33 days the patient received 8 gm. ammonium chloride daily and lost 1.4 kg. During this period the degree of extension of the right shoulder increased. The circumference of the right and left knees and the right and left ankles decreased without improvement of joint motion. Joint pains were decreased, and no medication was required.

For the next 7 days the patient received 8 gm. sodium bicarbonate daily. During this time she increased her weight 1.2 kg. The degree of extension of the right shoulder was again decreased to its original value. The circumferences of the knees and ankles again were increased. Edema of the face and of the dorsal surfaces of the hands developed. Joint pains became severe and required analgesics for their control.

For the next 6 days the patient again received 8 gm. ammonium chloride daily. Again her weight decreased, and the circumferences of the knees and ankles were decreased. Edema of the face and hands again disappeared. Joint pains were again relieved, and no analgesics were required.

Summary. Five females with typical rheumatoid arthritis were placed on a fixed diet and were given ammonium chloride and sodium bicarbonate while changes in their body water were estimated. With the loss of water induced by ammonium chloride there was in general a decrease in the pains and joint swelling and an increase in the joint mobility. These changes were reversed by the accumulation of water induced by sodium bicarbonate. It would appear that, in these cases at least, some of the symptoms of rheumatoid arthritis are altered to some degree by changes in the body water.

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SALMONELLA INFECTION IN INFANTS AND CHILDREN

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DUE to improved feeding techniques and milk control, infantile diarrheas no longer play the rôle they used to do in the earlier years of the century. However gastro-intestinal disturbances are still being observed in single instances as well as in epidemics. The causes of these gastro-intestinal disturbances have been ascribed to overfeeding of good food, to feeding of bad food, to infections in general, and to specific bacterial diseases with their principal symptoms in the intestinal tract. As in other countries, so in the United States, these intestinal cases with a distinct bacterial etiology have seemed to be on the increase, or perhaps we have a better technique in finding the cause. So there are increasing reports of

dysentery, especially of the Flexner type, being published. In addition a whole group of *Salmonella* (paratyphoid) infections are being brought to light in all countries in the world. This of course is especially important to pediatricians, and it is of this group of cases that we wish to make a short presentation.

Salmonella infections in infants and young children manifest themselves clinically either as diarrheas under the caption of gastro-enteritis, or as bacteremias with or without localization. Occasionally a mixed form is seen. The typhoid type occurring in adults and older children is rather unusual during the first years of life. The gastro-enteric form usually is accompanied by a fever of a non-specific type but not necessarily so. The stools are usually watery, but may be dysenteric in nature. The cases without temperature and with a few watery stools are, of course, very often not recognized. In fact this picture with or without temperature, with or without blood in the stool, can really only be diagnosed by careful bacteriologic examination. Of course, in the young infant the picture of alimentary intoxication may also supervene. The type with bacteremia or marked general infection may have any and all kinds of complications which occur in any bacteremic involvement in the young infant.

To obtain a fairly accurate idea of the rôle played by *Salmonella* infections in infantile diarrheas in a given locality, 3 factors are of importance. First, awareness of the possibility of such infection in any form of diarrhea in the individual case or in epidemics. Second, consistency in the search for the etiology, which means examining more than just an occasional specimen of the stool; and third, the use of proper laboratory technique consisting of the use of selective media, enrichment procedures, and serologic differentiation. Thus Hormaeche and co-workers,¹ examining stools of 1611 children in Montevideo, found in 395 cholera-like, dysentery-like diarrheas, or transition forms. In this group *Shigella* organisms were found in 32% and *Salmonellas* in 20%. Among the other cases with watery stools only, were 85 with *Salmonella* and 12 with *Shigella* in the stools. There were furthermore 11 cases with *Salmonellas* and 3 with *Shigellas* in the feces with no clinical symptoms whatever. Similar large-scale examinations have not been carried out elsewhere, yet it can be said that aside from possible numerical differences in this country, *Salmonella* infections are not an infrequent cause of infantile diarrhea.

Present Study. In a series of 369 cases of human *Salmonella* infections in North America and in Cuba, in which clinical information was available, the types of the organisms were classified by us at the New York *Salmonella* Center connected with this hospital. Fifty cultures came from infants and young children. The clinical picture was that of a septic infection in 9 cases, and in the remaining 41 children the predominant symptom was diarrhea.

The serologic *Salmonella* types found in these children were: Group B, *S. typhi murium*; Group C, *S. cholerae suis*, *S. oranienburg*, *S. bareilly*, *S. montevideo*, *S. newport*; Group D, *S. enteritidis*, *S. eastbourne*; Group E, *S. give*, *S. anatum*; Group F, *S. wichita*, *S. urbana*, *S. havana*, and *S. panama*. Eleven cases were due to *S. typhi murium* and 25 to organisms belonging in the serologic Group C of *Salmonella*. These two etiologic groups are the most numerous also among the adults in the series. There, however, *S. typhi murium* occurred twice as often as organisms of Group C. A greater susceptibility of infants and young children to infections with *S. suipestifer*, a representative of Group C, was assumed to exist by Gajzágó and Goettche.² This seems to be confirmed by our figures and extended to Group C as a whole.

Eight cases of *Salmonella* infections observed in our Pediatric Department within the past 3 years present several interesting features. There were 3 cases of simple gastro-enteritis due to *S. typhi murium* involving infants of 3 and 5 months and a 3-year-old child. A 10-year-old boy with enteric fever due to *S. paratyphi B* received sulfaguanidine for 40 days, but the stools were not freed from the organisms. A case of a purulent lesion and 1 of enteric fever due to *S. typhi murium* as well as 2 cases of infant diarrhea due to more unusual types of *Salmonella*, namely *S. newport* and *S. montevideo*, shall be described briefly.

In our experience, *S. typhi murium* is the most common type found in human *Salmonella* infections in this country and causes in 9 out of 10 cases a rather harmless gastro-enteritis. *S. newport* and *S. montevideo* represent each about 7% of the human infections in which we have examined the type. Both organisms belong in Group C of *Salmonella* and show a higher degree of invasiveness in man than *S. typhi murium*. They may cause enteric fever and septic infections aside from gastro-enteritis though not as frequently as *S. paratyphi B* and *S. cholerae suis* respectively.

Case Abstracts. CASE 1. M. G., an 11-months-old female (admitted 2/19/39) was operated on 5 weeks before for intussusception; reduction was performed. The child had fever between 101° and 104° for 2 days, was restless and had projectile vomiting 4 to 5 times a day. Three to 4 loose, greenish stools; benzidine test positive. There was a trace of acetone in the urine. Three days after admission the temperature rose to 105.4°. There was slight distention of the abdomen. The following day the abdomen was tympanitic, seemingly tender, there was diffuse resistance, but no masses were felt. A tap in the left lower quadrant revealed pus, from which *S. typhi murium* was cultured. The temperature dropped immediately after the paracentesis and the child was discharged much improved on 3/6/39. At no time were pathogenic organisms found in the feces.

CASE 2. A. L., a 5-year-old female (admitted 9/12/41) had fever for a month. During the first week of the fever she had 4 to 5 stools daily; no blood in them. She became afebrile on the second day in the hospital. Stools were examined on 9/12, 9/16 and 9/19 and found negative for pathogenic organisms. An agglutination test with the patient's serum on 9/15

was positive for *Paratyphoid B-O* in dilution 1:200, but negative with the specific phase flagellar antigen of *Paratyphoid B (b)*. However, a positive agglutination was obtained with the specific phase flagellar antigen of *S. typhi murium (i)*. The agglutinin titer for *S. typhi murium* in the patient's serum was 1:1600 on 9/20. Only from a stool specimen on 9/24 was *S. typhi murium* finally recovered.

CASE 3. R. S., 2 months old, female, admitted 10/5/40, born in London, had reached this country 2 weeks before; had not gained weight during the last 2 weeks; was emaciated; buttocks excoriated. The stools were mucoid, bloody on one occasion only. *S. newport* was cultured from the stool. After a blood transfusion and dietary treatment, the diarrhea was stopped a week after admission. The patient's serum agglutinated *S. newport* in a dilution 1:200. The mother's serum agglutinated the organism weakly in dilution 1:100. Her stools were negative for pathogenic organisms, she gave no history of enteric infection. Sulfanilamide, 5 gm. in all, sulfanilylguanidine 1.26 gm. per day for 8 days, and sulfathiazole 3.15 gm. did not free the stools from the *Salmonella* organism. A stool of the child obtained 8 months later, was positive for *S. newport*.

CASE 4. I. E., a 7½-months-old male, was admitted (12/2/40) because of diarrhea, fever and anorexia. He had had an attack of diarrhea 9 days before, which subsided within 4 days. The stool contained *S. montevideo*. Patient's serum agglutinated the organism in dilution 1:50. The stools were loose, contained specks of blood, became normal on the 5th day in the hospital. Sulfanilylguanidine was given for 12 days, stool cultures were still positive on discharge 12/21/40.

CASE 5. S. B., a 3-year-old male, was admitted (2/7/39) for cough and discharge from nose, for 1 week, temperature between 100° and 103.5°. Since 5 days, 6 to 10 loose yellowish-green stools—abdominal pain and vomiting. *S. typhi murium* was isolated from the stool, the patient's serum agglutinated this organism up to dilution 1:200. The temperature came down to normal on the 2nd day in the hospital, from the 3rd day on the child had 2 to 3 pasty brown stools.

CASE 6. E. L., a 5-month-old male, was admitted 2/13/39. The child had fever, cough and ear discharge for 6 weeks. Febrile temperature since 2 weeks; 6 to 8 watery stools within the last 24 hours. During the first 3 days in the hospital he had 4 to 5 loose yellow stools a day; on one occasion the feces were blood-streaked. *S. typhi murium* was found repeatedly in the stools; agglutination test with the patient's serum on 2/20/39 was negative.

CASE 7. N. L., a 3-month-old male, was admitted (10/6/39) because of fever and diarrhea for 5 days. Acutely ill, dry skin, hollow eyes. Bright red bloody stools. Clinical impression: dysentery. *S. typhi murium* in feces.

CASE 8. H. M., a 10-year-old male, was admitted 9/20/41; a refugee child; infected on a Spanish boat, had periumbilical pain and fever up to 104° for 3 days; constipation, anorexia. Spleen 1 finger below costal margin, few rose spots on 9/23. Septic temperatures—gradually decreasing until 12th day in hospital. *S. paratyphi B* from blood and stool. Agglutination with *S. paratyphi B* rose up to 1:1600. Sulfaguanidine for 40 days, positive stool cultures were obtained after discontinuation of the drug.

It is known that *Salmonella* infections tend to occur during the summer months. Yet none of these 8 cases fell into this season. No connection with other cases or carriers could be detected except for the case R. S., whose mother possibly had a subclinical infection. Contrary to the statements of most authors, a carrier state was

observed for a considerable length of time. It may be noted that the therapeutic use of sulfanilylguanidine proved ineffective in *Salmonella* infections not due to *S. paratyphi A* or *S. cholerae suis*.²

Summary. Routine cultural examination of a series of stool specimens from all infants and children with gastro-intestinal symptoms is suggested. Agglutination tests are not without value, although they are not always positive in cases of simple gastro-enteritis. According to Hormaeche they become positive more often in the dysentery-like cases than in other forms of enteritis. Nevertheless, in all doubtful infections of more than a week's duration, agglutination tests with a variety of *Salmonella* antigens should not be omitted. Blood cultures should also be taken if the syndrome is that of enteric fever or generalized septic infection.

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CYANIDE POISONING FROM CHOKE CHERRY SEED

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IN these western states, the numerous choke cherry trees yield berries, the pulp of which is used by some for jam-making and eaten raw in large quantities by campers—Indian and white alike. In instances where there exist great hunger or an injudicious appetite or craving, the fruit may be eaten whole, or the seed and pulp broken up in the mouth and swallowed indiscriminately.

The fresh pits of the choke cherry, *Prunus melanocarpa*, contain enough cyanide to be poisonous, perhaps lethal, to the consumer. This property is shared by the fresh pits of peach, prune, and several other similar plants.³ Among western Indians the choke cherry is an important dietary item during the months of August and September.

Although it is well known that the fresh peach seed is poisonous, very little attention has been given to the seeds of the wild choke cherry. A thorough search of the literature reveals but one publication on the subject. In Pardee's³ case (1847) certain singular features of his patient bear repetition: "A little boy about three years old had been in the habit, in the fall of 1846, of resorting with other boys to a tree of the wild choke cherry and of eating freely, and at all times, of the choke cherries, the tree being of easy access and being loaded with fruit, and the ground underneath being well covered with them. He seemed to have swallowed great numbers of them whole. One morning, while apparently in the enjoyment

of his usual health, he began to complain of pain in the epigastric region and soon after vomited and discharged quantities of whole cherries; he had convulsions, was drawn backwards, rolled his eyes about, and died in a short time, before any medical aid reached him. I made a postmortem examination on the day subsequent to his death and found, on opening the abdomen, that the stomach and intestines were of a dark, modena red color, such as would be caused by the juice of the wild cherry infiltrating through the walls of stomach and intestines. And on opening the alimentary canal, I found it literally filled with cherries in every condition—indeed, there were at least two quarts of cherries in the whole alimentary canal.”

Case Abstracts. CASE 1. Unfortunately, this case reported by Pardee was unknown to me when, in August of 1940, a 14 year old Indian school girl was admitted to the Western Shoshone Hospital. She was stuporous, had intermittent attacks of convulsions non-Jacksonian in character, was pale, cyanotic, her respirations labored, and a rectal temperature of 105°.

Physical examination revealed no contributory neurologic signs. There were equivocal Babinski reactions, but no Oppenheim or Gordon signs. The pupils were equal and reacted to light and accommodation. Although rolling of the eyeballs was present, the eyes presented no fixed deviation. Inability to coöperate prevented other neurologic studies. The chest was normal to percussion and auscultation, confirmed by a roentgenogram (Roentgen ray plates of the skull were normal), and a KB film of the abdomen revealed certain small circumscribed shadows, the interpretation of which was uncertain. The cerebrospinal fluid showed no abnormality, although the pressure was low.

The blood studies presented a white count of 14,200 (differential negative); red blood cell count of 2,800,000. The venous blood seemed to have a slight vermilion hue. There was a slight increase in the venous pressure (140 mm.); systolic arterial pressure, 76 mm. Hg; diastolic, 30. The pulse rate was 140; the heart sounds muffled, but well heard. The urine (by catheterization) was entirely negative, no acetone, acetoacetic acid, sugar, albumin, or microscopic abnormalities. The abdomen was soft, and there were no muscle responses to pressure palpation. Rectal examination was negative.

A continuous intravenous drip of 5% dextrose on Hartman's solution was started and no other form of treatment used. The patient died in 24 hours.

Autopsy (limited to the gastro-intestinal tract) revealed large quantities of choke cherries and broken seeds throughout the tract. The entire mucosa was deeply stained red by the cherries themselves. There was nothing else abnormal found in the gastro-intestinal system.

Inquiry disclosed that the patient had spent several days in the mountains, subsisting mainly on choke cherries,¹ and, apparently, in her hunger, had eaten huge quantities of cherries, in many instances breaking the seeds in her mouth. This point is stressed, as the ingestion of the broken fresh seeds is of paramount importance clinically.

E. V. A. Murphy, a visiting botanist, made the suggestion that members of the family rosaceæ, which includes choke cherries, contain seeds whose pits are poisonous and confirmed our impression that the choke cherry, like other members of this family, might produce hydrocyanic acid. It is well known¹ that cherry, almond, and peach seeds and leaves contain cyanophoric glucosides.

Fresh choke cherries were obtained and the pits removed, crushed and given to 3 guinea pigs. All of these animals died in convulsions. Here, then, was a poisonous substance at least lethal to guinea pigs, 2 gm. sufficing to produce death. The pits of seeds were then crushed, distilled in acid and the distillate absorbed in weak base. The distillate absorption (0.1 cc.) was lethal to guinea pigs within 8 minutes. Qualitative tests for cyanide were strongly positive. Lack of facilities rendered further assay impossible. It was apparent that this substance could be liberated from choke cherry seeds during acid hydrolysis in the stomach. Dried crushed seeds exposed to air apparently lost their toxic properties.

Numerous reports in the literature² indicate that the equivalent of 60 mg. of hydrocyanic acid may be fatal, but larger doses have been recovered from. The longer the patient is kept alive, the better his chances are for recovery, because the body detoxifies cyanide by combining it with methemoglobin and sulfur compounds to form stable and inactive sulphocyanates.

While it is true that cyanide combines with hemoglobin to form cyanhemoglobin, a non-oxygen bearing compound, this substance is formed slowly and in a small amount. Death is not due, primarily, to cyanhemoglobin or to a cyanide effect on the carotid sinus, but to its inhibition of cell respiration; the respiratory center in the medulla ceases to function because its nerve cells can no longer obtain oxygen for its respiration. Even though the blood is saturated with oxygen, the tissues are incapable of utilizing it.

Now, as the breakdown of cyanogenetic glucosides, of which the choke cherry amygdalin is one, is a slow process in the gastrointestinal tract, and as cyanhemoglobin is formed slowly, the treatment is directed along two channels: first, to cease ingestion of toxic material and, secondly, to remove all material already ingested from the gastro-intestinal tract.

Methylene blue is of no value therapeutically, and under some circumstances it can even hasten the reconversion of methemoglobin, a useful compound forming a stable substance with cyanide, to hemoglobin. Sodium thiosulphate and sodium nitrate are the safest agents to employ for methemoglobin formation in cyanide poisoning. However, these measures with occasional side toxic reactions are unnecessary if the cyanide-producing material is removed from the individual. This is demonstrated by the fact that 3 other cases were admitted during September, 1940, with symptoms of coma, convulsions, vasomotor collapse, labored respirations not of the Küssmaul type but more of a Cheyne-Stokes character, the skin having a suggestive pink cyanosis. Vomiting and epigastric pain were the early symptoms in all these cases. Treatment consisted of gastric lavage with weak sodium bicarbonate solution, repeated high enemata and the subsequent administration of 15% magnesium sulphate solution in large quantities through a Levine tube placed well into the duodenum. Lumbar punctures

were done in each case with a beneficial effect. Intravenous dextrose solutions and small transfusions were also helpful.

TABLE 1.—DATA ON 4 CASES OF CHOKE CHERRY SEED POISONING

Name	Age	Date	Admission temperature	Central nervous system	Neuro-muscular system	Vomiting as early symptom	Blood in G.I. contents	Treatment	Result
H. D.	12	8-24-40	105	Deep coma convulsions	Fibrillary muscular twitchings	+	+	None	Died
H. R.	15	8-30-40	101 ²	Stupor, cannot talk; semi-comatose	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.
P. T.	54	9- 2-40	100	Slight stupor, listless, barely able to talk	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.
C. R.	14	9-10-40	98 ⁴	Partial coma dizziness barely able to talk	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.

In these 3 cases the diagnosis would have been missed, the treatment ineffective and death unquestionably would have occurred, had we not ascertained the direct cause of the symptoms. There have probably been mild cases of choke cherry seed poisoning, the symptoms of which must have bewildered the physician. It is only by the ingestion of fresh crushed seeds that a toxemia is induced.

Conclusions. Four cases of poisoning from the ingested, fresh seed of the western choke cherry, *Prunus melanocarpa*, are presented. The fresh pit of this western choke cherry is said to contain cyanophoric glucosides which break down into hydrogen cyanide in the gastro-intestinal tract, producing hydrocyanide poisoning, which may be fatal. The treatment for this type of cyanide poisoning is also presented.

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THE EFFECT OF BENZEDRINE SULFATE IN MIGRAINE*

A PRELIMINARY REPORT

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THE purpose of this report is to describe the effectiveness of benzedrine sulfate† (amphetamine sulfate or beta-aminopropyl-

* Presented, in part, before the Illinois Psychiatric Society, Chicago, Ill., on Feb. 5, 1942.

† Benzedrine sulfate prepared for intravenous administration was kindly supplied by the Smith, Kline & French Laboratories, Philadelphia, Pa.

benzene sulfate) in the treatment of migraine. The results indicate that this drug may be a useful addition to the physicians' armamentarium for the treatment of this disease.

Regardless of the basic pathogenesis of migraine, evidence accumulated to the present time implicates a local disturbance of the arterial system, angiospasm or dilatation, as the immediate causal agent for a paroxysm. The studies of Wolff and his associates¹ indicate that dilatation and distention of cranial arteries which may be produced by a variety of factors form the basis of the headache. The effectiveness of ergotamine tartrate in adequate dosage in aborting, reducing or terminating an attack of migraine headache has been demonstrated consistently since its introduction by Lennox and von Storch in 1935.² This drug decreases the amplitude of the pulsations of the cranial arteries, chiefly certain branches of the external carotid artery.⁵ Its therapeutic effect depends presumably on its ability to produce prolonged and powerful vasoconstriction.

Unfortunately following the administration of ergotamine tartrate undesirable symptoms of a toxic nature frequently occur. Von Storch⁶ has discussed the limitations of this therapy. The commonest untoward reactions were nausea, vomiting, numbness and tingling of the hands and feet, muscular pains and muscular stiffness. These, if severe and prolonged, besides being decidedly unpleasant to the patient, may constitute a warning of impending arterial thrombosis. Other symptoms such as insomnia, restlessness, globus hystericus, choking sensations and precordial pain occur less frequently and, although alarming to the patient, do not seem dangerous. The occurrence of any of these accessory symptoms whether dangerous or not may be of such importance to the patient as to prevent the use of the drug for therapeutic purposes.

As a result a study was begun with the purpose of evaluating benzedrine sulfate as a possible therapeutic agent. This drug was selected because it is a sympathomimetic compound with a prolonged action. Vasoconstriction with its concomitant pressor effects was desired. It too decreases the amplitude of the pulsations of the cranial arteries.⁵ The increase in psychic function with a lessening of fatigue which this drug produces was thought possibly to be of value because slowness of thought and fatigue are frequently a part of the migraine syndrome. This drug can also produce undesirable reactions such as intense restlessness, inability to relax, insomnia and cardiac irregularity, depending upon individual idiosyncrasy. It is contraindicated for patients with cardiovascular disease, particularly those with hypertension. It must, therefore, be administered with due caution.

Benzedrine sulfate has been given previously to patients suffering from migraine, but not studied extensively. Nathanson³ in a study of the effects of benzedrine sulfate on fatigue had 4 subjects in his

series who complained of migraine attacks when they became easily tired. He was administering the drug orally in 10 mg. doses before breakfast and at noon. He found that the frequency of their migraine attacks lessened with amelioration of fatigue. In addition 1 patient was able to prevent the headache by taking 10 mg. by mouth during the prodromal stage. Palmer⁴ found it of no value in 3 cases. Sutherland and Wolff⁵ observed that an intramuscular injection of 10 mg. was sufficient to relieve the attack in 1 of 3 cases. Collectively then 10 patients have been reported as receiving this drug for their migraine. Two obtained relief from attacks, 3 others had the frequency of their attacks reduced while the remaining 5 were unaffected.

Procedure. Twenty-five patients suffering from typical migraine but free from other discernible disease form the basis for this study. If the patients reported to the hospital during an attack, the drug was administered intravenously in 3 to 20 mg. doses. The rate of injection was given cautiously, 1 mg. per minute for the first injection. Subsequently, if no untoward symptoms developed, the speed of injection was increased, reaching a maximum in 1 patient of 20 mg. in 3 minutes. The speed of injection was controlled according to the rise in blood pressure which was taken at minute intervals. An increase of 20 to 40 mm. Hg in the systolic blood pressure was used as the criterion. There was great variability among the patients in their sensitivity to the drug—the blood pressure arose abruptly in 2 patients after administration of but 3 mg. and 7 mg. intravenously. The injections were then discontinued because they were deemed dangerous.

Following testing of their response to intravenous medication, these patients were advised to take the drug orally in 10 to 40 mg. doses at the beginning of an attack. Seven patients who were examined between attacks were placed directly on oral medication. Three patients having very frequent and severe paroxysms were placed on oral medication daily at varying intervals up to every 4 hours in order to evaluate the drug as a prophylactic agent.

Results. The accompanying table presents the results and types of medication employed for the treatment of 25 patients suffering from migraine. Eighteen of these patients received benzedrine sulfate intravenously from 1 to 7 times for the relief of their migraine attacks. Twelve (67%) consistently obtained complete relief from their attacks in from 7 to 45 minutes. All of them were suffering in their attack near or at its height. The rapid disappearance of the symptoms was dramatic and startling. Most of the attacks were exceedingly severe with confusion being prominent in 3; 9 had complete relief of all symptoms; 2 usually had residual hyperesthesia over the affected side which gradually disappeared during the following 2 hours; and 1 usually had a dull residual lasting several hours which gradually faded away. Three of these 12 on some occasions had a recurrence of their symptoms after 4 hours. These subsequent symptoms were relieved by further intravenous administrations. Of the 6 patients who failed to obtain relief, 2 obtained relief regularly from ergotamine tartrate, 1 from oxygen therapy, but the other 3 failed to respond to any therapy employed.

The injection of benzedrine sulfate intravenously was approached with due caution. In our experience with complete control over the dosage there has been no serious reactions. The accompanying physiologic changes were fairly consistent qualitatively from patient to patient. There was an increase in the blood pressure of 15 to 40 mm. Hg in both the systolic and diastolic pressures which reached their maxima in 5 to 10 minutes after the injections were completed. An increase in blood pressure was found necessary in order to obtain relief and the rate of injection was controlled by the rise in blood pressure. The pressures then slowly fell until the original level was reached in 45 to 60 minutes. The pulse rate varied, increasing on some occasions but more commonly diminishing from 8 to 15 beats per minute at the height of the reaction. Pallor was common. Slight dilatation of the pupils occurred. Only 4 complained of feeling tense to the point where it was uncomfortable. Most of the patients remarked that they felt brighter and no longer fatigued. Insomnia, which had been anticipated as a possible complication did not occur and presented no particular problem. One patient reported greater ease in breathing as his nasal passages felt clear. Another stated his chest felt heavy and breathing was difficult. The most serious complication was a cardiac irregularity characterized by extrasystoles. This disappeared in 40 minutes. All symptoms of stimulation of the central and autonomic nervous systems had completely disappeared in 60 to 90 minutes. So in summary then there was only one possible serious toxic reaction—the cardiac irregularity out of a total of 51 intravenous injections. In the majority the reactions were so mild that discomfort was minimal.

As indicated in the accompanying table, 22 patients were given benzedrine sulfate to take by mouth in prescribed doses of 10 to 40 mg. at the onset of a migraine attack. Medication administered orally was not as successful as when given intravenously. Eight patients (36%) of the group obtained relief or had their paroxysms aborted in 30 to 60 minutes. In no case was oral medication effective, if the desired reaction could not be obtained by intravenous administration. In comparing quantitatively the severity of the paroxysms of the patients, it became apparent that those patients who obtained relief by oral medication suffered from typical but mild attacks. These patients reported a difference in their subjective response to the drug, depending upon whether it was taken at the time of an attack or on some other occasion. If taken during a paroxysm, toxic symptoms such as tension, restlessness, increased energy output and insomnia were usually less severe than on other occasions.

In contrast to the patients with mild and infrequent paroxysms were 3 cases at the opposite end of the scale, having frequent and severe attacks. They responded well to benzedrine sulfate when it

was given intravenously. The frequency of their paroxysms, however, was such a serious problem that it was decided to try the drug as a prophylactic agent. Small oral doses were administered frequently during the day in 2 cases and during the day and night in the third. A maintenance dose was found for each one of these patients which relieved them of their paroxysms, yet was not sufficient to cause toxic manifestations.

The most interesting patient from this viewpoint may be briefly presented:

CASE 1. She was a 34 year old married woman admitted to the hospital on May 16, 1941, because of severe migraine characterized by left-sided headaches, scotomata, nausea, vomiting and confusion occurring every 2 to 3 days. Of interest was the fact that her father, mother, 2 paternal aunts and 2 sisters suffered from typical migraine. In this patient those attacks had been present for many years and had completely incapacitated her for the preceding 11 years following the birth of her only child. The attacks could be controlled only by tremendous amounts of morphine and its derivatives or barbitol and its related compounds. For example, the day before admission she had been given 1 gr. morphine, 1 gr. pantopon and 12 gr. phenobarbital. Following admission, there was a prolonged severe reaction due to withdrawal of these drugs. After recovery from this, she began to have frequent severe paroxysms almost daily and was completely incapacitated. She was refractory to ergotamine tartrate as well as various analgesics and salicylates, but responded promptly to benzedrine sulfate when administered intravenously in 20 mg. doses. This large amount was necessary not only to relieve the individual attack but also to cause a blood pressure rise. She was then placed on oral medication in 10 mg. doses every 4 hours. At first the drug was taken at 6 A.M. and 10 A.M. Paroxysms then occurred only in the afternoons. The medication was then extended to 2 P.M. and 6 P.M. with the attacks then occurring during the night. Epinephrine in oil (2 cc.) was then added and injected intramuscularly at 10 P.M. resulting in complete relief for the patient. Finally benzedrine sulfate was substituted for the epinephrine, so that the total medication the patient was taking consisted of 10 mg. at 6 A.M., 10 A.M., 2 P.M. and 7.5 mg. at 6 P.M., 10 P.M. and 2 A.M. On this regime the patient has remained symptom-free. She has become a lively, enthusiastic woman able to resume her life in society which for the preceding 11 years she had been unable to do. She has had only one period of return of her severe paroxysms. This occurred when she exhausted her supply of medication and there was a delay in the replenishing of it.

Summary and Conclusions. Twenty-five patients suffering from migraine were treated symptomatically with benzedrine sulfate. Twelve of 18 patients (67%) had their attacks aborted quickly when the drug was administered intravenously. Eight of 22 patients (36%) obtained relief or had their paroxysms aborted when the drug was taken orally during the prodromal stage. Three patients having frequent and severe attacks became symptom-free when the drug was taken daily and in divided doses.

This evidence seems to indicate that benzedrine sulfate is useful in the treatment of migraine. It may be used as a substitute for ergotamine tartrate when the latter is either ineffective or productive

of severe toxic symptoms. It may be administered by mouth daily in repeated small amounts as a means of preventing attacks in those patients suffering from frequent and severe paroxysms.

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HYPOGLYCEMIA FOLLOWING ALCOHOLIC INTOXICATION

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In the past few years, we have seen a number of patients brought to the hospital in a state of hypoglycemic coma following alcoholic intoxication. It has been suspected that these patients had been drinking a denatured alcohol solvent sold locally under the name of "Solox," but in no instance has this been proved. Recently, Brown and Harvey³ reported the occurrence of hypoglycemia in drinkers of "smoke," a solvent identical in composition with "Solox." The clinical features of our cases have been similar in all respects to those reported by these authors. We have been unable to find any other account of this condition in the literature.

The recognition of this occasional cause of unconsciousness would appear to be a matter of importance. In our cases, treatment with glucose solution intravenously has resulted in rapid recovery. We think that death might readily occur in an untreated patient.

We have been able to add little to the observations of Brown and Harvey as to the cause of this type of hypoglycemia. In the hope that the condition may be more widely recognized and further light thrown on the nature of the disturbed metabolism, the following 4 cases are reported:

Case Reports. CASE 1. E. L., a white man, aged 33, was admitted to Memorial Hospital on December 31, 1936, unconscious and having convulsions. He had been drinking bootleg whisky for an indefinite time, and was known to have had several drinks before retiring at 9 A.M. the morning before admission. He had awakened at 7 P.M., and complained of feeling badly. In a short while he became unconscious. He was examined by a physician who found him relaxed, and thought him drunk. Shortly afterwards he began to have convulsions, was seen again by his physician, and sent to the hospital at 1 A.M.

On admission, the patient was completely unconscious, and having frequent tonic convulsions with opisthotonus. The pulse rate was 180, respirations were stertorous with a rate of 42, temperature 100.6° F (rectal), blood pressure 146 systolic, 68 diastolic. The pupils were dilated, but reacted to light. The neck was not stiff between convulsions. The extremities were flaccid between convulsions, and no tendon reflexes were obtained. The remainder of the examination was negative.

Urinalysis showed a specific gravity of 1.022, 2+ albumin, negative sugar, and positive acetone. There were occasional white and red cells, and many hyaline and granular casts in the urinary sediment. Blood counts showed 4.9 million erythrocytes, 96% hemoglobin, 20,000 leukocytes with 88% neutrophils, 8% lymphocytes and 4% monocytes. The blood sugar was 25 mg. per 100 cc., the non-protein nitrogen 50 mg. per 100 cc. The Kline test was negative.

It was at first thought that the patient might have strychnine poisoning. Gastric lavage was done, and large doses of sodium phenobarbital given hypodermically. This resulted in complete relaxation. Lumbar puncture revealed a clear fluid under 160 mm. pressure, containing 3 cells. When the report of the low blood sugar was obtained, 50 cc. of 50% glucose solution were given intravenously. Within a few minutes, the patient regained consciousness and asked for whisky. He remained conscious, and was able to take a liquid diet the following day. The blood sugar the morning after admission had risen to 224 mg. per 100 cc. His further course was uneventful, some sedation being given for restlessness. He was discharged on January 2, 1937.

CASE 2.—E. B., a negress, aged 35, was admitted to St. Philip Hospital on November 8, 1938, unconscious. She was known to have been a heavy drinker for many years, and 1 year previously had spent several months in a mental hospital. The reason for her commitment was not known. When seen, she was said to have been drinking for 4 days. She had been asleep off and on for 24 hours, and 4 hours before admission had become completely comatose, and could not be aroused at all.

The patient was of a very small stature and slight build (height 4 feet 7½ inches, weight 88 pounds). She was unconscious on admission, but roused slightly to painful stimuli. The temperature was 100.2° F. (rectal), pulse rate 110, respiratory rate 22; blood pressure, 125 systolic, 80 diastolic. The pupils were equal and reacted normally to light. The neck was not stiff. All extremities were held in rigid extension. The tendon reflexes were symmetrically hyperactive, and sustained ankle clonus and positive Babinski reflex were present bilaterally. The remainder of the examination was negative.

Urinalysis was entirely negative, including a negative test for acetone. Blood counts showed 5 million erythrocytes, 95% hemoglobin, 13,800 leukocytes with 73% neutrophils, 23% lymphocytes, 4% monocytes. The blood sugar was 20 mg. per 100 cc., the non-protein nitrogen 23 mg. per 100 cc. Blood Kline and Wassermann tests were positive.

Subarachnoid hemorrhage, or some other form of cerebral accident was suspected. A lumbar puncture revealed a clear spinal fluid which contained 14 cells, 6 neutrophils and 8 lymphocytes. Wassermann and mastie tests were negative. Hypoglycemia was not suspected until the low blood sugar was reported 2 hours after admission; then, 30 cc. of 50% glucose solution were given. The patient soon woke up in a rage. She talked at random all night, but was able to take liquids. The following morning, the blood sugar was again low, 56 mg. per 100 cc., and 2 days later 51 mg. The patient's mental status improved slowly. Two days after admission, she appeared to be entirely rational and otherwise well, and remained so.

Glucose tolerance tests (100 gm. of glucose by mouth) showed the following results: On November 11, 3 days after admission: 60 mg. (fasting),

116, 123 and 122 mg., in $\frac{1}{2}$, 1 and 2 hours respectively; on November 16: 74 mg. (fasting), 89, 70, 84, 80 and 73 mg., in $\frac{1}{2}$, 1, 2, 3 and 4 hours respectively; on November 21: 66 mg. (fasting), 70, 64, 50, 60, 60 and 64 mg., in $\frac{1}{2}$, 1, 2, 4, 5 and 6 hours respectively.

Roentgen ray of the skull showed the sella turcica to be normal, and the pineal body to be calcified and not shifted. On November 22 the basal metabolic rate was -25% . At this time the serum cholesterol was 210 mg. per 100 cc.

The patient was placed on desiccated thyroid, U.S.P., 2 gr. 3 times daily. She was discharged on November 26, to be followed in the out-patient department, but failed to return.

CASE 3.—J. D., a negro barber, aged 33, was first admitted to St. Philip Hospital on July 31, 1939, unconscious. He was known to be a chronic alcoholic, and was said to have been hospitalized elsewhere 1 year before for delirium tremens. He had begun drinking the day before admission, and had returned home at 1 P.M. the day of admission and gone to bed. At 7 P.M. his wife could not arouse him. He had remained comatose until brought to the hospital at 10 P.M. There had been no previous episodes of unconsciousness.

When seen, the patient was in profound coma, not responding to any stimuli. The temperature was 97° F. (rectal), pulse rate 68, respiratory rate 18, and blood pressure 140 systolic, 90 diastolic. The pupils were small, equal and reacted to light. The fundi were normal. The neck was not stiff. There were scattered rhonchi throughout the lungs. The extremities were flexible, but the tendon reflexes were uniformly hyperactive. A questionable Babinski reaction was present bilaterally. There was no ankle clonus. The nails of the fingers and toes were clubbed. The remainder of the examination was negative.

Urinalysis was negative except for a trace of acetone. Blood counts showed 4.4 million erythrocytes, 85% hemoglobin, 5200 leukocytes (66% neutrophils, 32% lymphocytes and 2% monocytes). The blood sugar was 25 mg. per 100 cc., the blood non-protein nitrogen 39 mg. per 100 cc. The Kline test was negative. Lumbar puncture revealed a clear spinal fluid under 80 mm. of pressure. There were no cells, and the spinal fluid Wassermann test was negative.

Hypoglycemia was suspected, and an intravenous infusion of 10% glucose solution was begun. The patient regained consciousness within a few minutes, and seemed fairly rational. He was given high carbohydrate liquid feedings, and remained fairly well until the second day when delirium tremens developed. This was controlled with large doses of barbiturates. The fasting blood sugar on the second day was 113 mg. per 100 cc. Glucose tolerance test (100 gm. of glucose by mouth) 1 week after admission showed the following blood sugar levels: 96 mg. (fasting), 91, 142, 105 and 57 mg. in $\frac{1}{2}$, 1, 2 and 4 hours respectively.

The liver edge, which had not been felt on admission, was subsequently found to be palpable 5 cm. below the right costal margin. No cause was found for the clubbing of the nails, which was stated to have been present since birth. The patient was discharged on August 19, 1939.

On November 16, 1940, 15 months later, the patient was again brought to the hospital unconscious. He had been found in this state in the hall of his rooming house. His wife had been separated from him for a year, and knew nothing of his recent activities. The patient subsequently stated that he had been drinking heavily for 4 months. The last thing he remembered was speaking to a friend in the rooming house about 12 hours before he was brought to the hospital. He could not remember when he had eaten last.

The patient was completely unconscious and ice cold. The temperature was not recorded; the pulse was irregular and feeble, with a rate of 86.

The blood pressure could not be obtained. The respiratory rate was 24. Both pupils were pinpoint, and did not react. The neck was not stiff. The lungs were clear, and the heart was not remarkable except for the irregular rhythm. The abdomen was held rigid. There was rigid spasticity of all extremities, with fine generalized convulsive tremors at times. The tendon reflexes at first could not be elicited because of spasticity, later they were uniformly hyperactive. The plantar reflexes were completely absent. The nails were clubbed.

Urinalysis was entirely negative, including a negative test for acetone. The blood counts were entirely normal. Blood taken at the time of admission showed blood sugar 32 mg. per 100 cc., blood non-protein nitrogen 36 mg. per 100 cc., total serum cholesterol 192 mg., esterified cholesterol 156 mg., and free cholesterol 36 mg. per 100 cc. The Kline test was negative.

Hot water bottles and blankets were applied to the patient's body, and, because of the previous history of hypoglycemia, 50 cc. of 50% glucose solution were given intravenously as soon as blood for chemistry had been drawn. The patient regained consciousness within a few minutes, and was able to take liquid nourishment. He remained rational thereafter. The fasting blood sugar level on the second day was 103 mg. per 100 cc.

After 3 days on a high carbohydrate diet, glucose tolerance test (50 gm. of glucose by mouth) showed the following blood sugar values: 101 mg. (fasting), 150, 156, 82, 87 and 89 mg. in $\frac{1}{2}$, 1, 2, 3 and 4 hours respectively.

Three days after admission, the patient complained of peculiar sensations and coldness in his feet. There was found to be a generalized hyperesthesia of both feet and ankles. The tendon reflexes were still hyperactive. A deficiency neuritis was suspected, and large doses of thiamin chloride were given parenterally, with gradual improvement in these symptoms. An electrocardiogram before thiamin was begun showed slight elevation of St_1 and St_2 with low voltage of all T waves.

Subsequent glucose tolerance tests were done (100 gm. of glucose by mouth). On November 29, the blood sugar levels were 95 mg. (fasting), 124, 130, 106, 74, 55 and 98 mg. in $\frac{1}{2}$, 1, 2, 3, 4 and 5 hours respectively. On December 10, the levels were 88 mg. (fasting), 122, 110, 110, 50 and 65 mg. in $\frac{1}{2}$, 1, 2, 3, 4 and 5 hours respectively.

In an attempt to demonstrate evidence of liver disease, other studies were undertaken. These were done, however, after several days on a high carbohydrate diet, and after thiamin had been given. The icteric index was 8 units. The serum phospholipids were 8 mg. per 100 cc. The oral hippuric acid excretion test⁶ (6 gm. of sodium benzoate by mouth) showed excretion of 3.2 gm. of hippuric acid in 4 hours. The intravenous hippuric acid excretion test⁷ (1.77 gm. of sodium benzoate intravenously) showed excretion of 1.28 gm. of hippuric acid in 1 hour. These results are not indicative of liver damage.

A Roentgen ray of the skull showed a normal sella turcica, and no other abnormalities. The basal metabolic rate was -6%.

The patient's further course was marked only by a respiratory infection. He was discharged on December 10, 1940.

CASE 4. H. J., a negro aged 41, was admitted to St. Philip Hospital on August 21, 1941, unconscious. He was a known chronic alcoholic. Subsequently it was learned that he had consumed a large quantity of whisky on the day before admission. He retired at midnight and arose at 6.30 A.M. the day of admission, and ate one sausage and a biscuit. His last recollection was of setting out for work. He was found unconscious on the street, and brought to the hospital at 8.45 A.M.

When seen, the patient was completely unconscious. The skin was cold but dry. Respirations were shallow with a rate of 15. The pulse was feeble and had a rate of 88. The temperature was 95.6° F. (rectal), and

the blood pressure 150 systolic, 100 diastolic. The pupils were constricted and equal. There was a slow side-to-side conjugate movement of the eyes. The lungs were filled with rhonchi. The extremities were flaccid; no tendon reflexes were elicited, and no pathologic reflexes were present.

Urinalysis was negative except for a 2+ acetone. The blood counts were not remarkable. The blood sugar on admission was 38 mg. per 100 cc., the blood non-protein nitrogen 36 mg. per 100 cc. The serum carbon dioxide combining power was 45.7 vol. %. The total serum cholesterol was 290 mg., esterified cholesterol 135 mg., and free cholesterol 55 mg. per 100 cc. The blood acetone body level¹ was 6.7 mg. per 100 cc. The Kline and Wassermann tests were positive.

Hypoglycemia was suspected, and the patient was given an intravenous infusion of 1500 cc. of 5% glucose in normal saline solution. He regained consciousness within a few minutes. He was able to take a high carbohydrate diet during the day of admission and thereafter. Because of suspected vitamin deficiency, thiamin, nicotinic acid and Brewer's yeast were also given. On the second morning, the fasting blood sugar level was 90 mg. per 100 cc.

On August 26, 5 days after admission, glucose tolerance test (100 gm. of glucose by mouth) showed the following levels: 109 mg. (fasting), 298, 186, 174, 102 and 95 mg. in $\frac{1}{2}$, 1, 2, 3 and 5 hours respectively. On August 29, an intravenous insulin tolerance test⁵ (0.1 units of regular insulin per kilo of body weight) showed the following blood sugar levels: 95 mg. (fasting), 60, 56, 71 and 77 mg. in 20 minutes, 1, $1\frac{1}{2}$ and 2 hours respectively. Adrenalin was then given intramuscularly (0.01 cc. of 1 to 1000 solution). Blood sugar levels of 90 and 91 mg. were obtained 45 and 60 minutes after adrenalin.

On August 22, the total serum protein was 8.2 gm., albumin 5 gm. and globulin 3.2 gm. per 100 cc. On August 28, an intravenous hippuric acid excretion test⁷ showed excretion of 0.28 gm. of hippuric acid in 1 hour. This is a subnormal excretion. A Roentgen ray of the skull showed a normal sella turcica, and no other abnormalities. The basal metabolic rate was +1%.

The patient's further course was uneventful, and he was discharged on August 30, 1941.

Comment. The histories of these patients are strikingly similar. In each case a known alcoholic had engaged in a recent bout of drinking. In every case unconsciousness came on 8 to 12 hours after the last known drinking, the patient frequently having slept overnight and awakened before lapsing into hypoglycemic unconsciousness.

Little reliable information could be obtained as to the amount of food recently taken. As with most alcoholics, it might be assumed that they had eaten little.

In the cases of Brown and Harvey, 3 of the 6 patients gave a history of drinking "smoke," a denatured alcohol solvent containing methyl alcohol, gasoline and ethyl acetate. It is well known that an identical preparation sold under the name of "Solox"* is widely

* According to the manual of the United States Industrial Chemical Company, "Solox" is the trade name for a shellac solvent manufactured in accordance with the following formula: Denatured alcohol formula No. 1, 100 gallons; ethyl acetate, 5 gallons; aviation gasoline, 1 gallon. Denatured alcohol formula No. 1 is prepared by adding 5 gallons of methyl alcohol to 100 gallons of 190 proof commercial ethyl alcohol.

used in Richmond as a beverage. It was suspected that all of our patients had been drinking "Solox," but, in spite of considerable effort spent in questioning them, its use could not be established. One of the patients had been drinking bootleg whisky. Another insisted he had drunk only "store whisky." It is likely that the use of "Solox" would be denied because of fear of legal complications.

The physical findings in our cases were similar to those in the Baltimore cases, and were essentially the findings of hypoglycemic coma.⁶ All the patients were totally unconscious. In none of our cases was an alcoholic breath odor described. This may be explained by the interval between the last drinking and the onset of hypoglycemic symptoms. The usual neurologic finding was extensor rigidity of all extremities, with increased tendon reflexes. In 1 case, there were fine convulsive twitchings, and in 1, repeated convulsions with opisthotonus. One patient showed flaccid limbs, and no tendon reflexes could be obtained. Conjugate side-to-side movement of the eyes was present in 1 patient. The findings were such that a cerebral accident, particularly subarachnoid hemorrhage, was suspected in most of the cases.

The diagnosis was established by the finding of a very low blood sugar level. In the later cases, glucose was given before the blood sugar levels were reported, and the immediate response established the diagnosis of hypoglycemia. The only other significant laboratory finding on admission was the presence of acetonuria in 3 of the 4 cases, and an elevation of the blood acetone bodies in the 1 case in which this was determined.

In all but 1 of the patients, the response to glucose was immediate, and complete, no relapses occurring. One patient (Case 2) did not recover completely for 2 days. This patient showed other findings that indicated a more fundamental disorder of carbohydrate metabolism, which will be discussed.

Several lines of thought presented themselves when an attempt was made to explain the cause of the hypoglycemia.

First, it was suspected that these patients might have an inherent abnormality of carbohydrate metabolism, hypoglycemia being precipitated by low food intake. The occurrence of repeated attacks in the same individual, both in our cases and in the Baltimore cases, suggested this. Such an abnormality would probably involve an endocrine dyscrasia. The endocrine system was investigated in 3 of the 4 patients. In Case 2, the small stature of the patient, flat glucose tolerance curves, and low basal metabolic rate were definitely suggestive of hypopituitarism. Unfortunately, other studies were not carried out, but it seems very likely that this patient had the "hypoglycemic unresponsiveness" associated with anterior pituitary insufficiency,⁵ and that severe hypoglycemia was precipitated by alcoholism and starvation. In the other 2 patients studied, there was no evidence of any endocrine abnormality. The glucose toler-

ance curve was normal in 1, slightly hyperglycemic in 1, and an insulin tolerance test normal in 1. These tests were done after recovery, but should demonstrate any inherent metabolic defect present. Basal metabolic rates were normal, and Roentgen rays of the sella turcica showed no suggestion of pituitary tumor.

The question of liver disease with impaired capacity for glycogen storage was considered. All the patients were chronic alcoholics, and might be expected to have some liver damage. In the 2 patients in whom tests of liver function were done, there was questionable evidence of impaired function in 1. In Case 4 there was diminished excretion of hippuric acid, and the hyperglycemic glucose tolerance curve might be considered as suggestive of liver damage.⁴ The serum cholesterol and cholesterol esters were normal, as were the total and fractional proteins. In Case 3 all the liver function tests were normal. Brown and Harvey noted questionable impairment of liver function in 1 of 6 patients. In both groups of cases, most of the studies were done after recovery, and do not indicate the state of liver function on admission. However, it does seem that there is little evidence of any residual liver damage, and that any changes present must have been transient.

In 1 patient, there was a suggestion of vitamin deficiency in the development of symptoms of peripheral neuritis, and thiamin was given. However, we are not aware of any association between deficiency of any of the known vitamins and hypoglycemia. None of the other patients showed any manifestations of deficiency.

Diminished food intake and depletion of liver glycogen may well have been a factor in the development of hypoglycemia in these patients. However, moderate periods of starvation do not lead to severe hypoglycemia.² Nor do the great majority of alcoholic patients, many of whom have eaten little, show any such lowering of the blood sugar.

The transient nature of the hypoglycemia and the absence of evidence of endocrine dyscrasia or of liver disease following recovery, suggest that a toxic factor is responsible. It seems likely that these patients had been drinking some form of denatured alcohol, and that one of the denaturing substances present is responsible for the hypoglycemia. Brown and Harvey were unable to demonstrate lowering of the blood sugar in dogs that were fasted for 48 hours, and given "smoke" by stomach tube. Perhaps a longer period of intoxication is necessary to reproduce the picture seen clinically.

The nature of the disturbance of carbohydrate metabolism is not known. We are inclined to agree with the suggestion of Brown and Harvey that there is interference with gluconeogenesis. The blood sugar of a fasting individual is maintained after depletion of the original glycogen stores by the continued release into the blood of carbohydrate formed from protein in the liver.² It seems plausible that in these patients, either because of temporary damage to liver

function generally or by specific inhibition of gluconeogenesis by the toxic substance, this conversion is prevented, and hypoglycemia results. The ketonemia and ketonuria observed are probably similar to those seen in other forms of hypoglycemia with or without depletion of liver glycogen,⁹ and are thought to be due to excessive breakdown of fat in the liver accompanying increased hepatic glycogenolysis.

Conclusions. 1. Four cases of hypoglycemic coma following alcoholic intoxication are reported.

2. It could not be established what these patients had been drinking.

3. In each case hypoglycemia occurred 8 to 12 hours after the last drinking.

4. The usual clinical manifestations were unconsciousness and extensor rigidity of the limbs with increased tendon reflexes.

5. All the patients recovered when glucose solution was given intravenously.

6. One of the patients was thought to have hypopituitarism. The other patients showed no evidence of any endocrinologic disorder.

7. Following recovery, there was only questionable evidence of impaired liver function in 1 patient.

8. The possible presence in the alcoholic mixture consumed of a substance having a toxic effect on carbohydrate metabolism is discussed.

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DETOXIFICATION OF PROGESTERONE DERIVATIVES IN THE LIVER*

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THE liver is the essential organ for the detoxification of estrogens^{11,13,16,21,25} and other steroids, especially progesterone.²⁰ Since pregnanediol is considered the end-product of progesterone metab-

* This investigation was supported by a grant from the John and Mary Markle Foundation.

olism in man,²³ it was thought that this compound might escape detoxification by the liver. This possibility was examined by comparing the activity of pregnanediol in normal and hepatectomized animals. But the results did not necessarily indicate a true detoxification by the liver. Therefore several other possible interpretations of the results were examined such as storage of the steroids in the liver, excretion into the bile, and so on.

Experimental Results. The activity of pregnanediol was compared in two groups of 5 young female rats weighing about 30 gm.; in the first group the animals were hepatectomized by the Selye and Waelsch method, which removes 75% of the liver;²¹ the animals in the other group were used as controls. As a test of the activity of pregnanediol, we used the anesthetic power evidenced by this steroid when it is administered by the intraperitoneal route.¹⁹ A single injection of 20 mg. of pregnanediol in 1 cc. of peanut oil was given to rats partially hepatectomized 3 hours previously and to their normal controls. A parallel experiment was performed with pregnanedione, a possible intermediary between progesterone and pregnanediol. A dose of 5 mg. of pregnanedione in 0.25 cc. of peanut oil was administered intraperitoneally to 5 normal and 5 partially hepatectomized female rats weighing about 50 gm. The results (Table 1) showed a much greater anesthetic activity of the 2 steroids in the partially hepatectomized rats.

TABLE 1.—INFLUENCE OF PARTIAL HEPATECTOMY ON ANESTHETIC ACTIVITY OF PROGESTERONE DERIVATIVES

	Intraperitoneal dose (mg.)	Degree of anesthesia.	
		Intact animals	Partially hepatectomized animals
Progesterone (after Selye)	5	Light	Deep
Pregnanediol	20	None	Light
Pregnanedione	5	Trace	Deep

The reduction in anesthetic activity by the liver may be due to its location in the path of absorption of the steroids since they were intraperitoneally injected. To answer this question, advantage was taken of the fact that, alone among steroids, pregnanedione produces anesthesia even when injected subcutaneously.¹⁹ Five or 10 mg. of this compound were given by the subcutaneous route to normal and partially hepatectomized rats weighing about 50 gm. The difference between the two groups of animals (Table 2) was as marked as in the preceding experiments (Table 1). The anesthesia after removal of the liver lasted over 24 hours and even in one case 51 hours. In the normal controls, there were either no symptoms at all or only a slight excitement in the 2 hours after the injection.

TABLE 2.—INFLUENCE OF PARTIAL HEPATECTOMY ON ACTIVITY OF PREGNANEDIONE GIVEN SUBCUTANEOUSLY

Dose	Degree of anesthesia.	
	Intact animals	Partially hepatectomized animals
5 mg.	None or trace	Deep
10 mg.	Trace	Deep

The possibility that steroids might be stored in the liver without being destroyed was examined by analyzing the extracts from the livers of animals treated with pregnanediol or pregnanedione. Aqueous and ether-alcohol extracts¹⁴ of the liver were tested for the presence of steroids, by intra-

peritoneal injection into partially hepatectomized rats. In the case of pregnanedione, three groups of 4, 7, and 11 rats weighing about 50 gm. received 5 mg. of this compound per animal subcutaneously and were sacrificed at 24, 36 and 48 hours, respectively, after the injection. It must be noted that 24 hours after the injection of the same dose of pregnanedione, hepatectomized rats are in deep anesthesia and their organism is therefore flooded with the steroid. If in the normal animals the steroid were stored in the liver, there would be enough hormone in the liver to induce sleep in a partially hepatectomized rat. However, the pooled extracts of 4, 7 or 11 rats, respectively, did not anesthetize one partially hepatectomized rat. Similar negative results were obtained in one experiment with the livers of 5 rats given pregnanedione.

The possibility that the effect was due to the elimination of the steroids in the bile was examined by preventing bile excretion surgically. The two main branches of the bile duct were ligated as closely as possible to the liver in a group of 6 young 50 gm. rats. In addition a third ligature was placed on the main bile duct formed by the junction of the branches. Bile pigments appeared soon in the urine of these animals, indicating interruption of bile secretion by the liver. After checking for the presence of pigment in the urine, a subcutaneous injection of 5 mg. of pregnanedione was given to the animals 24 hours after the operation. In spite of the absence of biliary excretion, no anesthesia was produced, while in intact animals given the same dose of the compound marked narcosis ensued.

Discussion. As long as the increased effectiveness of pregnanediol or pregnanedione after partial hepatectomy was observed only after intraperitoneal administration, it was not an absolute proof of the detoxification of these substances in the liver. It appeared possible that the liver reduced the activity of the steroids only when they were absorbed through the portal vein. When the ability of the liver to inactivate steroids has been observed *in vivo*, it was usually after intraperitoneal administration. Thus Golden and Sevringhaus observed that ovaries transplanted to the mesentery did not induce estrus in spayed females.⁸ If later on the same ovaries were placed in the axilla, estrus appeared. Similarly Biskind and Mark found a reduction in the activity of pellets of estrone or testosterone implanted in the spleen, while these pellets were active when placed outside the peritoneal cavity.² Evans and Burr with estrone,⁵ Segaloff and Nelson with estradiol,¹⁸ Albrieux and colleagues with progesterone,^{1*} Fels with estrone and stilbestrol,⁶ reported likewise a smaller activity by peritoneal than by subcutaneous administration. It was important to decide whether the liver could also reduce the activity of steroids administered otherwise than intraperitoneally. Subcutaneous administration of pregnanedione to normal and partially hepatectomized animals (Table 2) demonstrated that partial removal of the liver greatly enhanced the activity of the steroid. Therefore the liver decreased the activity of pregnanedione, whatever the path of absorption may be. The quoted experiments^{1,2,5,6,8,18} simply indicate that the ability of the

* Recently Fels and Monaco⁷ observed no inactivation of progesterone by the liver, contrary to well-established results of Selye²⁰ and others.¹

liver to reduce the activity of steroids is more easily exerted in case of absorption through the portal system.

The liver may act on the steroids in three different ways. The compounds are either inactivated by the liver cells (true detoxification), or excreted into the bile, or stored in the liver and released too slowly for their effect to be exerted. Such a storage of the steroids in liver cells, similar to what has been found in the case of cholesterol itself,¹⁷ could explain the reduction in the anesthetic power of the steroid in presence of the liver, since the intrahepatic accumulation of the compound would prevent the flooding of the steroid in the body, necessary for anesthesia.¹⁹ However, the investigations performed with extract of livers showed no anesthetic activity and therefore no accumulation of steroids in that organ.

The possibility of excretion of steroids into the bile was indicated by the finding of estrogens in that fluid.^{4,9,10,12} When fairly large amounts of estrogens were injected, only a small percentage of the administered amount, namely 13%²² or from 1 to 8%¹⁵ could be found in the bile. Such a small biliary excretion could not account for the large increase in the activity of the steroids after removal of the liver. A recent report by Cantarow, A., Rakoff, A. E., Paschkis, K. E., and Hansen, L. P.,³ indicates that the intravenous injection of very large doses of estrone is followed by a marked excretion of estrogen in the bile. The method of injection and the magnitude of the amounts used are such as to explain the discrepancy between their results and those of other investigators. Indeed our experimental results showed that, in the absence of bile excretion, the liver completely retained its ability to reduce the activity of the steroids.

The only remaining possibility is that of an inactivation, that is to say, a true detoxification of the steroids by the liver tissue. *In vitro* experiments with other steroids led to the same conclusion: thus, estrogens were reported to be destroyed by a liver mash^{11,25} or by perfusion through the liver.¹³

Conclusions. 1. Free pregnanediol is detoxified in the liver.

2. Experiments with pregnanediol and pregnanedione indicate that detoxification of these substances by the liver is not essentially dependent upon the path of absorption; it is not due to storage in the liver or to excretion in the bile, but is the result of an inactivation by the liver cells.

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A NEW CONCEPT OF THE CAUSE OF PATENCY OF THE DUCTUS ARTERIOSUS*

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THE cause of closure of the ductus arteriosus is a problem which is both fundamental and important to our knowledge of physiology of the fetus at birth and to our understanding of one of the common forms of congenital heart disease, patency of the ductus arteriosus. Yet, this problem has remained unsolved and largely unexplored by experimental research until recently.

There have been many theories put forward to explain the mechanism of closure of the ductus arteriosus, but for the most part these have not been supported by experimentally observed facts. Wells in 1908³ summarized the more important of these theories of closure as follows: the expansion of the large bronchi at the onset of breathing compresses the ductus arteriosus; thrombosis in its lumen and subsequent adhesion of the walls closes the ductus; bending of the arch of the aorta by increased pressure after birth causes closure; beginning of respiration causes a change in position of the thoracic

* Read before the Annual Meeting of the American Federation for Clinical Research, Minneapolis, Minn., April 20, 1942.

viscera and this causes tension and collapse of the ductus; fibrous growth in the intima leads to occlusion; active contraction of the layers of the wall of the ductus closes it; fibrous bands passing over the ductus are connected with the diaphragm and upon descent of the diaphragm with respiration the bands are pulled down and occlude the ductus; a thin crescentic fold of tissue present at the aortic end of the ductus acts like a valve in preventing the flow of blood from the aorta into the ductus.

Wells had a clear conception of the conditions that must be satisfied for any theory of closure to be valid. He wrote (p. 388) that closure of the ductus "is a physiological process taking place spontaneously and instantaneously in every newborn child, and therefore there must be some mechanism which can be relied upon always to perform this occlusion. Any explanation which involves connective tissue proliferation must be inadequate, for the duct is patent and carrying on its full function up to the moment of delivery, and then is at once occluded when the child begins to breathe; it is necessary to distinguish between the instantaneous occlusion of the duct and its subsequent obliteration."

We have recently presented experimental work which clarifies to some extent the mechanism of closure of the ductus arteriosus (Kennedy and Clark^{1,2}), and which forms a basis for a new concept of the cause of patency of the ductus arteriosus.

Using guinea pigs we have found that closure of the ductus normally occurs in two distinct phases: the first is a muscular contraction of the wall of the ductus requiring several minutes, following this the ductus remains closed. The second phase consists essentially in replacement of the muscular tissue in the wall by fibrous connective tissue, resulting in the ligamentum arteriosum. The latter process requires about 1 month in the guinea pig.

Near the end of fetal life the ductus arteriosus is a potentially contractile structure which remains open during fetal life as far as we have observed. However, it has the ability to close in response to various stimuli, to remain closed during continuation of the stimulus, and under certain conditions, to open again after the stimulus has ceased. Under the proper circumstances this sequence of closure and opening can be repeated many times. Mechanical or electrical stimulation of its wall or of nearby tissue will cause it to close promptly within about 1 minute.

Other than mechanical or electrical stimulation, the most reliable stimulus to closure is breathing or intermittent inflation of the lungs with air. In our experiments the onset of normal breathing after birth was always followed by closure of the ductus arteriosus in from 3 to 10 minutes. Inflating the lungs with intermittent puffs of air through a tracheal cannula (in order to simulate breathing artificially) causes closure of the ductus in healthy fetuses within several minutes.

We have also observed closure of the ductus following injection of adrenalin, following mechanical stimulation of the carotid sinus, and after the fetus had experienced a brisk hemorrhage.

It seems likely that under physiologic conditions breathing is the most important cause of closure.

In our artificial breathing experiments (inflation of lungs through a tracheal cannula) we found that when air or pure oxygen is used closure occurs regularly; however, when pure nitrogen is used (oxygen being rigidly excluded from the gas used for inflation), the ductus fails to close. Our observations indicate that oxygen is a necessary component of the inflation mixture for closure to occur. In view of these results, it occurred to us that the introduction of oxygen by a route other than the lungs might cause closure. Without inflating the lungs, oxygen was injected slowly in tiny bubbles into the umbilical vein. This resulted in closure of the ductus.

Our observations have led us to a new concept of the ductus arteriosus. It is a potentially mobile structure and is able to actively close by contraction of its muscular wall in response to certain definite stimuli, much as many other hollow, smooth muscle structures. Under the conditions of our experiments, if the stimulus ceases, the ductus will open again. This active muscular contraction with obliteration of the lumen is the first phase of closure of the ductus arteriosus and occurs during the first few minutes following birth, under normal circumstances, beginning with establishment of effective respiration. In normal animals the ductus remains closed after this initial closure and is finally transformed into the ligamentum arteriosum (Kennedy and Clark¹).

We believe that it is the interruption of the first phase or the initial closure that causes patency of the ductus arteriosus. In other words it is an interruption of a normally occurring or physiologic process, not some bizarre malformation, which produces this type of congenital heart disease when it occurs unassociated with any other defect.

We have observed patency of the ductus arteriosus, under certain conditions, in guinea pigs which lived several hours after birth.

It is our opinion based upon these experiments, although we are unable to offer direct evidence to support it, that vigorous respiration with high concentrations of oxygen just after birth will promote the prompt closure of the ductus arteriosus in humans.

It seems appropriate here to point out that an approach to this problem through its pathology is inadequate; that is, a study based wholly on postmortem specimens will not give the observer an accurate idea of the true state of the ductus during life. Many times during our experiments we have seen a ductus arteriosus, which was open at the time of the animal's death, close as a result of dissection in the vicinity of the ductus several minutes or longer after death. We have also occasionally observed a ductus arteriosus

which was closed at the time of death, open subsequently, in each instance under abnormal conditions.

We wish to hold up for condemnation the practice of the pathologists in many hospitals of inserting a probe into the ductus arteriosus, especially in the newborn, in order to ascertain whether it is open or closed. Anyone at all familiar with the histologic changes in the ductus following birth realizes that such a procedure is entirely worthless. We are unwilling to accept any data relative to closure of the ductus in which the patency of the ductus was tested in this way.

It should be emphasized that the ductus arteriosus in late fetal life is potentially a mobile or contractile structure and will respond by closure to certain stimuli much the same as many other hollow muscular structures. Therefore, we believe that the problem of closure must be studied by means of a physiologic approach.

Summary. The cause of closure of the ductus arteriosus at birth is important to our knowledge of physiology and of heart disease.

Our observations on guinea pigs show that the ductus is different from the other great arteries both histologically and in its physiologic reactions.

The ductus arteriosus during late fetal life is potentially an active structure and is able to close in response to certain definite stimuli.

It normally closes within the few minutes following birth and remains closed. If this normal process of closure is interrupted, patency of ductus arteriosus results. Thus, it may be the interruption of a normal physiologic process which causes this form of congenital heart disease when it occurs alone, not some bizarre malformation.

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ABNORMALITIES OF THE AMOUNT OF THE CIRCULATION (HYPER- AND HYPOKINEMIA) AND THEIR RELATION TO NEUROCIRCULATORY ASTHENIA AND KINDRED DIAGNOSES*†

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For the last 15 years we have been accumulating data on the amount of the circulation of subjects lying at rest, both normal

* This paper was presented before the Association of American Physicians in May, 1942.

† The completion of this work was assisted by a grant from the Daland Fund of the American Philosophical Society.

persons and patients from the medical wards. At first we employed the ethyl iodide method,³ in recent years the ballistocardiograph,⁴ and about 1600 of these records have been taken. These were filed under appropriate diagnoses and, with the passage of time, certain files have become full enough to warrant detailed analysis of their contents. One of these files contains the records of 68 cases characterized by symptoms referable to the circulation which could not be accounted for by any abnormality demonstrated by the usual hospital procedures; the group usually classified under such vague diagnoses as functional heart disease, neurocirculatory asthenia, autonomic imbalance, sympathicotonia, vagotonia and the like.

By estimating the cardiac output, functional abnormalities of the circulation have been discovered in many of these cases. But, as similar changes have also been found in many patients with organic disease, to enable readers to see the subject of this study in proper perspective it will first be necessary to trace the history of our investigations and to review the state of the circulation found in other clinical conditions.

The first step in the classification of our data was to discover the normal standards for the amount of the circulation,⁵ the second was to divide the abnormal cases into two groups: those with circulations above and below normal. This approach has been and still is used to classify and to interpret data concerning blood pressure. When one thus studies the circulation one needs a term to serve the same purpose as the term hypertension, and it was not easy to find a satisfactory word.

One could say that a patient had a "supernormal circulation" or that he suffered from a "supernormal circulatory" state, but such terms seem long and awkward. The term "supercirculation" reminds one unpleasantly of Hollywood; while "hypercirculation," of mixed etomological parentage, derives dignity only by relation to its half-brother "hypertension" whose history certainly shows that a bar sinister is no bar to a place of importance in our language. Turning to the Greek roots "hyperrrheaemia," increased flow of blood, proved too difficult to pronounce differently from the familiar "hyperemia." Eventually the term "hyperkinemia," increased motion of blood, was suggested by Dr. J. H. Austin. Easy to say and with a short adjective form, the terms hyperkinemia and hypokinemia have been adopted to indicate the corresponding abnormalities of the amount of the circulation when estimated with the subjects at rest in the supine position.

About 2 years ago our data on the first 100 cases with hypokinemia were published.⁶ In Table 1 these data have been reviewed and amplified.

The first two items in this table are based on inferences. Hypokinemia is to be expected in any moribund subject because, in becoming zero at death, the circulation must pass through a hypo-

kinemic stage. There seems to be ample evidence from animal experiments to expect hypokinemia in cases of shock, but this is another inference for we have not worked on shock.

TABLE 1.—OCCURRENCE OF HYPOKINEMIA

Group.	Frequency of hypokinemia among all cases in this group
Moribund patients	All
Shock	All ?
In congestive heart failure	Most
Valvular heart disease not in failure	About 1/2
Coronary heart disease:	
Chronic angina pectoris	Almost all
Soon after infarction	About 1/2
Hypertension	About 1/3
Endocrine diseases:	
Myxedema	All
Pituitary or adrenal	Many
Convalescence from severe febrile disease	About 3/4
Essential hypokinemia	26 cases

Our data show that hypokinemia is to be found in most, but by no means all, cases of congestive heart failure. Of the cases of valvular heart disease not in failure the abnormality is encountered frequently, chiefly in those who have been in failure or who are in danger of it. In chronic angina pectoris hypokinemia is the rule and its presence often provides welcome objective evidence of the presence of this condition. Over one-third of the cases of hypertension show hypokinemia, chiefly those with small hearts. Severe cases of certain endocrine diseases usually have it. It is very common in convalescence from the severe acute infections. Finally in our data are 26 cases in which hypokinemia was found without any disease to which it could be attributed, and these cases fall into the group which is the subject of this study.

It took almost 3 years longer to assemble 100 cases with hyperkinemia and our first publication on this subject is now in press.⁷ The results pertinent to this discussion have been summarized in Table 2.

TABLE 2.—OCCURRENCE OF HYPERKINEMIA

Group	Frequency of hyperkinemia among all cases in the group
Healthy persons	A very few
Hyperthyroidism without cardiac complications	Almost all
Extreme emaciation	About 3/4
Patent ductus arteriosus	Most
Peripheral A-V aneurisms	Few
Anemia	About 1/4
Febrile disease tested late in the course	A few only
Hypertension	A very few
Pulmonary:	
After pneumonectomy	4 of 5 cases
In chronic disease	A few
Essential hyperkinemia	20 cases

In analyzing the hyperkinemic group there is a difficulty which is absent when hypokinemia is studied. Excitement may cause

hyperkinemia in anyone, therefore an isolated instance is of no importance. The occurrence of 16 instances of the abnormality in tests of over 400 healthy persons can be accounted for partly by excitement in class demonstrations, partly by chance cumulation of inherent errors; for, working with methods containing errors which we believe to be large, one has no right to expect a perfect division between normal and abnormal. In the healthy group, whenever the test was repeated, the second value was normal, a fact which distinguishes this group from those to follow.

Almost all cases of hyperthyroidism without obvious cardiac involvement show hyperkinemia, as is well known.

The hyperkinemia of emaciated persons is partly a matter of definition, for their circulations were above normal in relation to their present body weight, not to what they should have weighed.

Most of our cases of patent ductus arteriosus had hyperkinemia, as has been found by others; but only one of 4 cases of traumatic peripheral arteriovenous communications showed this abnormality. Doubtless it is a matter of the size of the communication.

In cases of anemia with hemoglobin under 60%, hyperkinemia was found less frequently than the literature had led us to expect. This was also the case in the febrile diseases. Stimulation of the circulation during the fever following the administration of pyrogens is easily demonstrated, but only 1 of 8 cases tested during the later half of a febrile disease showed hyperkinemia.

The few cases with hypertension who also had hyperkinemia formed a consistent group. All were extremely ill and all but one had marked cardiac hypertrophy.

We were surprised to find hyperkinemia in 4 of 5 cases after surgical removal of one lung, and we have encountered it rarely in chronic pulmonary disease. Hyperkinemia was also found in 7 cases with nothing in common which we could discover and, as excitement may cause this abnormality in anyone, such isolated instances deserve no attention.

Finally, in our data are 20 cases in which no reason for the abnormality was discovered, and these cases fall into the group which is the subject of this study.

Let us stop to compare these cases of essential hyperkinemia with the corresponding hypokinemic group. Figure 1 shows that the distinction is not difficult when their ballistocardiograms are available. The symptoms of these 2 patients were rather similar; I have little doubt that most of us would have been content to classify them under the same heading. But the difference in the impacts of their circulations was so very great that the physiologic mechanisms at fault must certainly have been very different.

A comparison of the clinical pictures of the two groups is given in Table 3. Both consist chiefly of young adults who think of themselves as nervous, but then the similarity becomes less marked.

The hypOS are weak and dizzy; they complain of dyspnea on exertion, and about one-fourth of them are subject to repeated fainting attacks. The hypERS deny weakness, dizziness is a minor factor, and there is no fainting among them. Indeed they do not usually

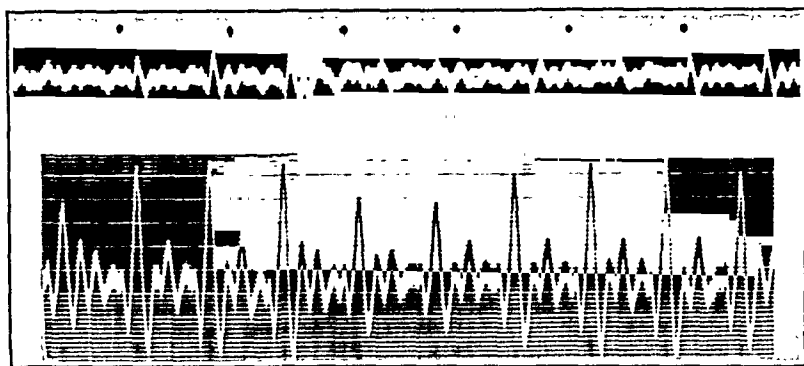


FIG. 1.—Ballistocardiograms from a hypokinemic patient (top) and a hyperkinemic patient (bottom). The time, in seconds, is indicated over the top record. Both records were taken with the subject horizontal after 15 minutes' rest. Reproductions one-half actual size.

Top.—E. G., a woman aged 46, wt. 151, B.P. 140/90, CC (chief complaint): Repeated fainting attacks. P.E. negative: orthodiagram, heart normal size; EKG normal. Cardiac output -30% .

Bottom.—J. D., a man aged 25, wt. 147 pounds, B.P. 150/70. CC: Spells of faintness not confined to upright position. P.E. negative. B.M.R. $+13$. Cardiac output $+57\%$.

think of themselves as ill, although they are underweight and tend to have rapid heart rates. An experienced clinician, inspecting cases of essential hypokinemia, gets no very definite impression about the diagnosis, but the patients with essential hyperkinemia are immediately suspected of having hyperthyroidism and only after repeated estimations of basal metabolic rate is this diagnosis abandoned.

TABLE 3.—SYMPTOMS IN ESSENTIAL HYPO- AND HYPERKINEMIA

	HypO	HypER
Average age, years	36	32
Deviation from ideal weight, pounds	+6	-13
Average pulse rate	74	90
Symptoms—Nervous	++	++
Weak	+++	0
Dizzy	+++	+
Fainting	+	0
Dyspnea on exertion	+++	+
Average B.M.R., %	-8	-3
First impression	?	Hyperthyroidism

The two groups which we have called essential hyper- and hypokinemia, characterized by these abnormalities of the resting circulations, without any known pathologic change to account for them, comprise two-thirds of the group which is the subject of this study, or 46 out of a total of 68 cases. The remaining 22 cases, without

any abnormality of the circulation detected at rest, must now be considered.

Seven of these cases exhibited the symptoms of weakness and dizziness, and the proneness to fainting attacks characteristic of the essential hypokinemic group. In these the resting circulation, although not subnormal, was exactly on the lower limit of normal. Since our estimates of the amount of the circulation include errors which we believe to be large, a perfect division between normal and abnormal cannot be expected. Therefore we have had no hesitation in adding these cases to the essential hypokinemic group.

The remaining 15 cases have less in common. Seven were characterized by having all their symptoms in attacks, they considered themselves well and free of symptoms between these episodes. But the attacks were of various characters; spells of weakness and faintness, and attacks of palpitation were most common. All these cases were diagnosed neuroses and in some the neurotic origin of the symptoms seemed obvious. Thus a coal miner, subject to attacks of shortness of breath without obvious cause, gave the history that his best friend had recently been invalided by silicosis.

Four of these 15 cases gave lifelong histories of neurotic manifestations; 2 were chronic neurasthenics, one had a history of over 30 admissions to the hospital.

In the 4 remaining cases, although their circulations were normal when they lay at rest, we were able to demonstrate a circulatory abnormality of another type by means of a test which has been studied only recently and therefore was not applied to the great majority of the cases in this series.

If a healthy person, after lying down for 15 minutes, arises and stands still, the circulation diminishes for approximately the first minute of standing and then remains constant for 10 minutes or longer. Therefore to compare the lying and standing circulations of our subjects we took records after 15 minutes rest horizontal, and $2\frac{1}{2}$ minutes after arising. In most subjects tested the impacts of each heart beat diminished after arising but the heart rate increased. When the circulation per minute was calculated these changes tended to cancel each other, the ratio of the lying to the standing circulation averaging 1 to 1 in 50 healthy persons.

Figure 2 illustrates ballistic records obtained both lying and standing in 1 healthy person and 3 of our patients. Evidently some of our patients were unable to make this adaptation properly; when they arose, not only the rate but also the output per beat was much increased, so that the relation of their circulation in the two positions was profoundly abnormal. It was while the cardiac output was abnormally elevated that these subjects had symptoms such as dizziness and faintness, a finding contrary both to my expectations and to the viewpoint generally taught. Apparently these patients suffer from an incoördination of the circula-

tion, a failure to adapt it to the needs of the situation in a normal manner. I am hopeful that such demonstrations will aid in explaining the symptoms of some of the cases in which nothing abnormal is disclosed by either the ordinary clinical examination, or an estimation of the resting circulation.

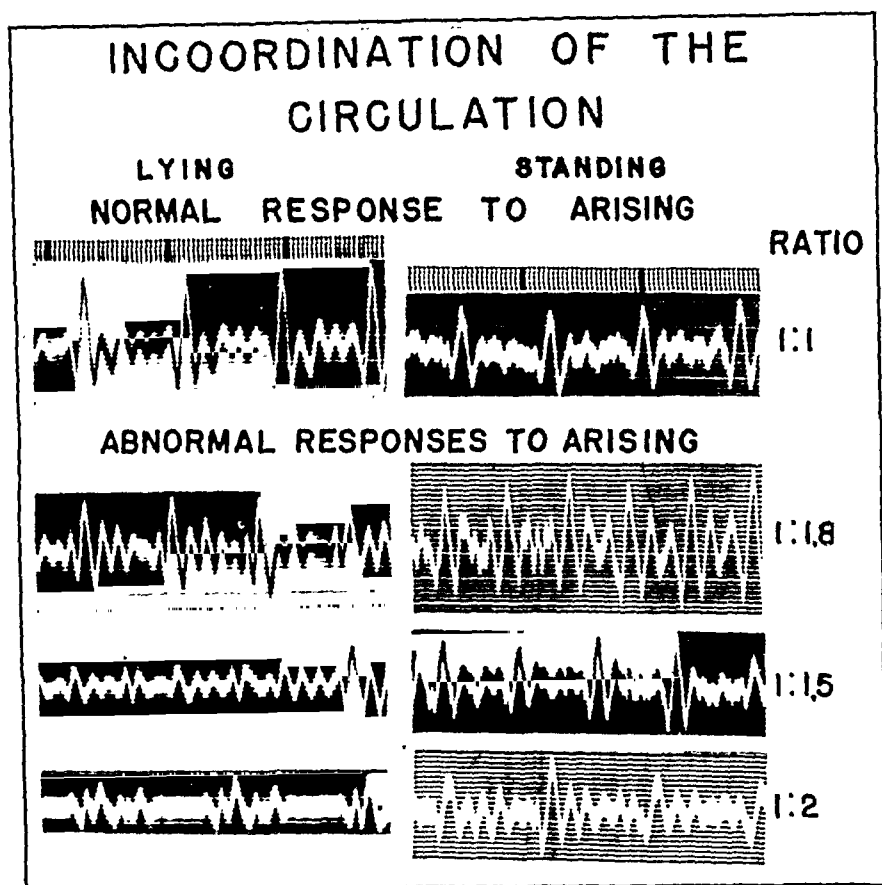


FIG. 2.—Ballistocardiograms after 15 minutes' rest horizontal and about 2 minutes after arising. The time record on the top applies to all the records, largest interval is equal to 1 second. The reproductions are one-half actual size.

Top row. M. T., a normal young woman aged 25, 5 feet 4½ inches, 140 pounds, B.P. lying 135/85, standing 135/90. Cardiac output both lying and standing does not deviate from the normal average.

Second row. F. W., a man of 36, 5 feet 9½ inches, 126 pounds, B.P. lying 114/88, standing 122/98. Studies all negative. CC: Dizziness on arising, fear of falling when upright. Cardiac output +13% lying, +100% standing.

Third row. P. M., a woman aged 42, 5 feet 3 inches, 128 pounds, B.P. 130/90 lying, 120/100 standing. All studies negative. CC: Palpitation, dyspnea on exertion, choking attacks at night. Cardiac output lying -17%, standing +22%.

Fourth row. P. C., a man aged 56, 5 feet 10 inches, 113 pounds, B.P. lying 112/68, standing 107/78. P.E. negative except that patient is very thin. CC: Fainting attacks especially in summer. Cardiac output lying -22% when referred to his actual weight, but -30% if referred to what he should weigh. C.C. standing +56% referred to actual weight.

We can conclude, therefore, that the great group of patients with symptoms referable to their circulations, but without disease

demonstrated by the usual clinical tests, can be properly divided into three sub-groups depending on the condition of their resting circulations. In the hyper- and hypokinemic groups, and in a few patients of the normokinemic group, we have demonstrated an abnormality of function which may well be the cause of many of their characteristic symptoms.

Patients with essential hypokinemia have resting circulations similar to those found in many cases of organic heart disease. Therefore it is not surprising that these two groups share many symptoms and that such a term as functional heart disease, which recognizes the similarity, has arisen. Certainly such symptoms as dyspnea on exertion, weakness, dizziness when upright, and susceptibility to fainting attacks, are consistent with the findings of subnormal circulation.

Patients with essential hyperkinemia share their circulatory abnormality with cases of hyperthyroidism, and it is not surprising that they have much the same appearance to gross inspection. Apparently the characteristic appearance of hyperthyroidism, so readily recognized at a glance by experienced clinicians, is more nearly related to the circulation than to the metabolic rate. Perhaps this is why patients with hyperthyroidism complicated by a cardiac disease which has reduced their circulation, may pass so long unrecognized. Without hyperkinemia the characteristic appearance is missing and the attending physician does not immediately see the need of an estimation of basal metabolic rate.

Our task would not be complete without an attempt to fit the older conceptions and terminology into the picture of the essential kinemic abnormalities. I must start by admitting that I, myself, have been diagnosing all these cases either neurocirculatory asthenia or cardiac neurosis without discrimination, and I believe that this is the common practice. Nevertheless, it is possible that others may have had more discrimination than I, for the older terminology may be fitted into the newer conceptions.

My cases with hyperkinemia seem entirely similar to the soldiers in the last war described by Peabody, Wearn, and Tompkins,² who called the condition "irritable heart;" and many readers will recall the controversy with Harlow Brooks as to whether they were really cases of hyperthyroidism. In civil life similar cases have been described by Kessel and Hyman¹ under the name "autonomic imbalance," and in Europe under such names as "parabasadowism" and "sympathicotonia." For cases with hypokinemia the term "neurocirculatory asthenia" is quite descriptive, and I suspect that the term "vagotonia" has also been used to characterize such patients. The term "cardiac neurosis" might be reserved for the normokinemic group. But such an attempt to unite the new and old conceptions would lead to great confusion in the minds of many who have fixed ideas as to what such terms mean.

There is a great deal to be said for a purely functional classification based on the most fundamental physiologic abnormality yet demonstrated. Therefore I propose to subdivide the patients with symptoms referable to their circulation, but without heart disease, into hypo-, hyper- and normokinemic groups, until better knowledge can provide an etiologic classification.

As in the case of hypertension, it is the ability to measure the abnormality which permits an investigation of its etiology to begin.

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THE EFFECT OF FOOD AND ALKALI ON THE ABSORPTION AND EXCRETION OF SULFONAMIDE DRUGS AFTER ORAL AND DUODENAL ADMINISTRATION

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A NUMBER of factors are known to alter the absorption of sulfonamide drugs from the gastro-intestinal tract, both in experimental animals and in man. Administration in the form of the sodium salts,^{3,11,13,17} or the simultaneous administration of sodium bicarbonate or magnesium oxide¹ increases the absorption of some of the commonly used sulfonamides. It has also been shown that sodium sulfapyridine is absorbed more rapidly and more completely in a subject with achlorhydria than when hydrochloric acid is present.¹¹ Conjugation with certain substances, including glucose,¹⁵ guanidine,⁷ succinyllic acid¹⁰ or acetic acid^{4,13} produces compounds which are poorly absorbed when given orally. This decreased

absorption is not related to solubility since the resulting compounds, except in the case of the acetyl derivative, are much more soluble than the parent drugs. Marked and unexplained individual differences in absorption of sulfonamide drugs have been noted frequently, both during actual therapy of patients with infections and in the course of studies in normal subjects.

It is known that sulfanilamide differs somewhat from its common derivatives with respect to absorption and excretion. Most striking is the comparatively good absorption of sulfanilamide from the rectum, whereas very little sulfapyridine, sulfathiazole or sulfadiazine is absorbed from this site.^{9,13,16,17} Stead and Kunkel¹² found that the maximum blood concentration of sulfanilamide occurred in 10 to 13 minutes after a 1% solution was put directly into the duodenum. It has also been shown that sulfapyridine delays the emptying time of the stomach in human subjects.⁸

In this paper are presented the results of studies on absorption and excretion of a single dose of several sulfonamide drugs in normal human subjects after oral and after duodenal administration. The effects of a meal, of the simultaneous administration of sodium bicarbonate and of administration in the form of the sodium salt were also studied.

Materials and Methods. The subjects were healthy ambulatory males from 16 to 60 years old. A 5 gm. dose was given in all experiments. Tap water (500 ml.) was given with the drug and approximately 150 ml. of fluids per hour was given throughout the first day. All the urine passed during the first 72 hours was collected and the amount of drug excreted in this period was used as an index of the amount absorbed. The drugs were given as powdered suspensions or as solutions in water. Drug levels in blood were determined at appropriate intervals by the method of Bratton and Marshall.² In the studies on "fasting" subjects, all food was withheld from the time of the evening meal (about 5 P.M.) until the drug was given, between 8 and 9 A.M. the next day, and breakfast was given from 1 to 2 hours after the drug. Sodium bicarbonate, when used, was given with the sulfonamide in 5 gm. amounts. Duodenal administration was accomplished through a Rehfuess' tube, the position of which was verified fluoroscopically. Several experiments were done in each subject, although not all the different experiments were carried out in any given subject. Two or more days were permitted to elapse after the urine was completely free of sulfonamide drugs before starting another experiment.

Studies with Sulfanilamide (See Table 1). When a single 5 gm. dose of sulfanilamide was given before breakfast, absorption was very rapid. The maximum blood concentration was high and was obtained at the time when the first sample was drawn, namely after $\frac{1}{2}$ hour. About 75% of the administered drug was recovered from the urine in 72 hours. Similar results were obtained when this drug was given directly into the duodenum. When the same amount of drug was given after breakfast, absorption was delayed, the maximum blood level was lower and the amount of drug recov-

ered in the urine in 72 hours was slightly greater. A 5 gm. dose of sodium bicarbonate given with the drug after a meal had no effect.

TABLE 1.—MAXIMUM BLOOD LEVELS AND URINARY EXCRETION AFTER A SINGLE 5-GM DOSE OF SULFANILAMIDE

Mode of administration.	No. of subjects.	Maximum blood concentration.		% of administered dose recovered in urine in 72 hours.*
		Mg. per 100 ml. (total*).	Hours after administration.	
Oral; before breakfast	3	10	$\frac{1}{2}$	76
Oral; after breakfast	2	8.1	3	82
Oral + NaHCO ₃ ; after breakfast	1	7.8	3	80
Duodenal; before breakfast	2	10.2	$\frac{1}{2}$	76

* Mean values.

A Comparison of Oral and Duodenal Administration of Sulfapyridine, Sulfathiazole and Sulfadiazine. These 3 drugs were handled quite differently than sulfanilamide when given directly into the duodenum. This is seen from the data summarized in Table 2. Absorption was much more rapid after duodenal as compared with oral administration. The maximum blood concentrations of these drugs when given by duodenum were reached early, namely in 1 hour in the case of sulfathiazole and in 3 hours in the case of sulfapyridine and sulfadiazine. The maximum levels, however, were considerably lower than when the corresponding drugs were given by mouth. Furthermore, the amount of drug recovered in the urine in the first 72 hours after the duodenal administration was only about one-half of the amount that was recovered when the same amount of drug was given by mouth.

TABLE 2.—ORAL VERSUS DUODENAL ADMINISTRATION OF A SINGLE 5-GM. DOSE OF SULFAPYRIDINE, SULFATHIAZOLE AND SULFADIAZINE

Drug.	Route.*	No. of subjects.	Maximum blood concentration.		% of administered dose recovered in urine in 72 hours.†
			Mg. per 100 ml. (total†).	Hours after administration.	
Sulfapyridine	Oral	2	7.7	6	70
	Duodenal	2	2.2	3	42
Sulfathiazole	Oral	3	6.7	3	68
	Duodenal	3	2.8	1	34
Sulfadiazine	Oral	4	5.5	7	54
	Duodenal	6	3.2	3	30

* All doses given before breakfast.

† Mean values.

Further attempts were made to influence the absorption after duodenal administration. The simultaneous administration of the patient's own fasting gastric juice, or of 80 ml. of N/10 hydrochloric acid or of an equal amount of sodium bicarbonate were tried in individual subjects, but none of these procedures had any effect on the maximum blood levels or on the amount of drug recovered from the urine. When the dose was divided and given in 4 equal

parts over a period of $1\frac{1}{2}$ hours, there was a slight increase in the amount recovered in the urine, as was shown to be the case with sulfaguanidine given orally in this manner.⁷

The Effect of Alkali and of Administration After a Meal on the Absorption and Excretion of Sulfadiazine. The remaining studies were carried out with sulfadiazine and sodium sulfadiazine and are summarized in Table 3. The highest and lowest values obtained in different subjects are noted and give some idea of the individual variations observed. The mean values of the blood levels and of the cumulative urinary excretions obtained at different times following the administration of a 5 gm. dose of sulfadiazine given in different ways are shown graphically in Figure 1.

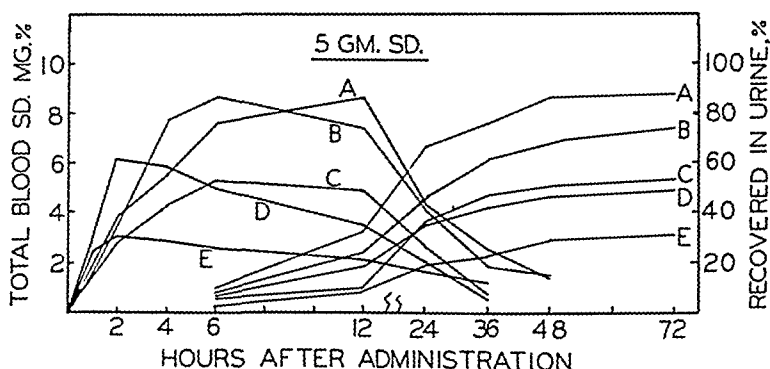


FIG. 1.—“Total” sulfadiazine blood concentrations and cumulative urinary recoveries after administration of a single 5-gm. dose of sulfadiazine in human subjects (mean values). A, Oral + NaHCO_3 ; after breakfast. B, Oral; after breakfast. C, Oral; before breakfast. D, Oral + NaHCO_3 ; before breakfast. E, Duodenal.

When sulfadiazine was given by mouth before a meal it was absorbed much better than after instillation into the duodenum. The maximum blood levels, although attained later, were almost twice as high after oral as after duodenal administration, and the amount of drug recovered from the urine in 72 hours was almost twice as great. The addition of an equal amount of sodium bicarbonate to the sulfadiazine given by mouth to the fasting subjects resulted in a decided acceleration of the absorption. The maximum blood levels were appreciably higher and were attained much sooner than when the drug was given alone. The amounts recovered in the urine in 72 hours, however, were about the same regardless of whether or not the alkali was given. Similar results were obtained with sulfathiazole by Barlow and Climenko.¹

When the dose of sulfadiazine was given after the morning meal, absorption was consistently more complete. The maximum blood levels were higher than in the subjects who received the drug before

a meal, even with bicarbonate of soda, and on the average about 25% more of the drug was recovered from the urine. The administration of sodium bicarbonate with the dose of sulfadiazine given after a meal seemed to have a delaying effect on absorption of the drug in the 2 subjects studied.* The maximum levels were about the same but they were attained somewhat later, and the total amount recovered from the urine was appreciably greater, averaging 92% of the administered dose.

Results with Sodium Sulfadiazine. In general, the sodium salts of sulfapyridine, sulfathiazole and sulfadiazine are absorbed more rapidly than their respective free acids when administered orally.^{3,11,13,17} The results of the present studies with sodium sulfadiazine are summarized in the lower part of Table 3.

TABLE 3.—MAXIMUM BLOOD CONCENTRATIONS AND URINARY EXCRETION OF A SINGLE 5-GM. DOSE OF SULFADIAZINE: EFFECT OF ADMINISTRATION WITH ALKALI OR AFTER A MEAL

Mode of administration	No. of subjects	Maximum blood concentration.						% of administered dose recovered in urine in 72 hours.		
		Mg. per 100 ml. (total)			Hours after administration					
		High	Low	Mean	High	Low	Mean	High	Low	Mean
Duodenal; before breakfast	6	3.8	2.1	3.2	6	2	3	32	26	30
Oral; before breakfast	4	6.6	3.9	5.5	12	4	7	70	30	54
Oral + NaHCO ₃ ; before breakfast .	3	8.4	5.5	6.9	3*	2	2	84	24	48
Oral; after breakfast	5	9.6	7.3	8.7	6	4*	6	86	61	77
Oral + NaHCO ₃ ; after breakfast .	2	9.0	8.2	8.6	12	12	12	96	85	92
Sodium sulfadiazine.										
Duodenal; before breakfast	1	17.6	$\frac{1}{2}$	86
Oral; before breakfast	3	16.0	15.2	15.5	14*	$\frac{1}{2}$	$\frac{1}{2}$	86	74	80
Oral; after breakfast	3	15.0	6.8	10.2	3	3	3	78	60	67

* This result was obtained in only 1 of the subjects.

When sodium sulfadiazine was given before breakfast, either orally or into the duodenum, absorption was very rapid. The maximum blood level was usually attained within $\frac{1}{2}$ hour, the time when the first blood sample was drawn. The blood concentrations at this time were all more than 15 mg. per 100 ml. This is comparable to the levels observed shortly after intravenous administration of the same dose.⁹ If due allowance is made for the sodium content of the administered drug, the urinary recoveries were also similar to those obtained following intravenous administration. When the sodium sulfadiazine was given after breakfast, the results were somewhat similar to those noted with sulfanilamide. Absorption was delayed, but in this instance it was less complete. The maximum blood levels were lower and were attained later, and an appreciably smaller amount of drug was recovered from the urine.

* It is to be noted that no blood samples were obtained between 6 and 12 hours, so that the maximum levels probably occurred within this period and probably were higher than the maximum observed.

Individual variations were greater when the dose followed the meal than when it was given before breakfast.

The subjects used in this study had free hydrochloric acid in their fasting stomach. The pH of the 1% sodium sulfadiazine solutions used was between 9 and 9.5. Three experiments were done *in vitro* with such solutions to determine the effect of adding dilute hydrochloric acid. It was found that most of the drug was precipitated out of solution between pH 7.5 and 8.0. More than 90% of the dissolved drug was precipitated, presumably as the free acid, at pH 7.5. Although gastric juice containing free hydrochloric acid has been shown to have some buffering effect,¹¹ it is very likely that the pH of the gastric contents in the present experiments was lower than 7.5 and that, for the most part, the free acid was precipitated out from the administered sodium salt in the stomach.

Observations on Abnormal Subjects. There was an opportunity to study the absorption of a single oral dose of sulfadiazine in a patient with non-tropical sprue. The blood levels attained were low and only 20% of the administered drug was recovered from the urine. A vitamin A absorption test done at the same time showed that this substance was likewise poorly absorbed. In a patient with pernicious anemia, sulfadiazine given orally before breakfast was found to be well absorbed. The maximum blood level was 9.6 mg. per 100 ml., 6 hours after administration of 5 gm., and 87% of the dose was recovered from the urine.

Discussion. Perhaps the most interesting fact brought out in these studies is the poor absorption of sulfapyridine, sulfathiazole and sulfadiazine after duodenal administration, as compared with the absorption of the same drugs when given orally. This is in marked contrast to the rapid and almost complete absorption after duodenal administration of sulfanilamide and sodium sulfadiazine, and probably also of the sodium salts of sulfathiazole and sulfapyridine, although these were not studied. It is only reasonable to assume that the portion of the sulfapyridine, sulfathiazole and sulfadiazine not excreted in the urine is largely found unchanged in the large bowel. From there, these drugs are poorly absorbed,^{9,13,17} and eventually are eliminated in the stools. It is suggested, therefore, that where large bowel bacteriostasis is desired it may be more advantageous to give such highly effective drugs as sulfathiazole or sulfadiazine directly into the duodenum, in preference to the less effective sulfaguanidine by mouth. The concentration of the former drugs in the feces after oral administration has been found to be low.⁵

The effect of giving a dose of drug after a meal was to delay absorption in every instance. With respect to the total amount absorbed, as reflected in the amount recovered in the urine, the effect of taking a meal shortly before the drug varied with the com-

pound used. With sulfanilamide there appeared to be little or no effect; with sulfadiazine the total amount recovered in the urine was appreciably greater and with sodium sulfadiazine the urinary recovery was slightly less (after allowing for the sodium content of the administered drug) than when the dose was taken on a fasting stomach. The explanation of these differences is not apparent.

The effect of food and of alkali on the absorption and excretion would seem to explain at least some of the discrepancies noted in clinical and experimental studies. It is likely that the kind of food ingested has a decided influence both on absorption and conjugation of sulfonamides, as indicated in some recent reports,^{6,14} but this aspect was not investigated.

The amounts present as "free" and as "total" drug were determined on every sample. All of the values mentioned in the text represent "total" drug values. The amount of drug excreted in the conjugated form in different experiments varied from 17 to 25% of the total at 12 hours and from 22 to 35% of the total in 72 hours. The differences in the amount of conjugation observed following various modes of administration were too inconstant to permit any deductions.

Summary and Conclusions. 1. Sulfanilamide is absorbed very rapidly and completely when it is given orally or into the duodenum. Food delays absorption of the drug but does not diminish the amount excreted in the urine.

2. Sulfapyridine, sulfathiazole and sulfadiazine are poorly absorbed from the duodenum.

3. Sulfadiazine is absorbed more slowly but more completely when it is given after a meal than if it is given on a fasting stomach. Alkali appears to increase the amount of drug absorbed when it is given with sulfadiazine after a meal. Sodium bicarbonate hastens the absorption of sulfadiazine when given on an empty stomach, but does not increase the amount absorbed.

4. Sodium sulfadiazine is rapidly absorbed from the duodenum or after oral administration in a fasting subject. Absorption is delayed and is less complete if it is given after a meal.

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BOOK REVIEWS AND NOTICES

THE MODERN ATTACK ON TUBERCULOSIS. By HENRY D. CHADWICK, M.D., Medical Director of Middlesex Tuberculosis Sanatorium; Formerly Commissioner of Public Health of the Commonwealth of Massachusetts, and ALTON S. POPE, M.D., Deputy Commissioner of Public Health and Director of the Division of Tuberculosis, Commonwealth of Massachusetts. Pp. 95; 5 figures and 8 tables. New York: Commonwealth Fund, 1942. Price, \$1.00.

THIS is an excellent review of the principles and to some extent the practices that have played a part in reducing tuberculosis morbidity and mortality in the United States. The book will be of value chiefly to public health officers and administrators. It contains chapters on the epidemiologic aspects of tuberculosis, diagnostic procedures, case finding, and the rôle of the sanatorium in control and treatment. The final chapter deals with various phases of an adequate community campaign for the eradication of tuberculosis. Naturally, in a book of this length it is not possible to discuss in detail methods of diagnosis and treatment of tuberculosis.

H. H.

ACUTE INJURIES OF THE HEAD. By G. F. ROWBOTHAM, B.Sc. (MANCH.), F.R.C.S. (ENG.). Pp. 288; 124 illustrations. Baltimore: Williams & Wilkins Company, 1942. Price, \$6.00.

THE publication of this book is timely, for all members of the medical profession whether or not in military service should have an authoritative source for consultation upon the proper treatment of cranial injuries. The author has had experience with air-raid casualties and hence brings to his readers the problems inherent in the treatment of this rather special type of casualty. After a discussion of the mechanism of injuries of the head in which, in discussing fractures, the point is made that it is not the injury to the bone but to the brain that is important, the various types of closed cerebral lesions are described together with their underlying pathology. Concussion and compression are the commonest causes for a fatality, and death occurs usually within the first 24 hours following injury. Contusions, lacerations and hemorrhage are the 3 primary lesions of the brain following injury, all due in these closed lesions to abrupt movement of the brain within the skull. The diagnosis and treatment of such injuries are thoroughly discussed and the Reviewer was pleased to note that the suggestion was forcefully made that, when in doubt as to the position or type of the lesion, prompt recourse be had to exploratory trephines or air injection. Chapter IV is especially valuable, for it describes in detail and lays stress upon the pre- and postoperative care of such cases, together with an outline of the proper surgical technique. In Chapter V the methods of handling open or compound wounds are described, together with considerable advice about the treatment of air-raid casualties. The illustrations in the chapter on the technique used in the management of compound fractures are valuable. The final chapters are devoted to the results of injury to special parts of the brain and to the sequels to injuries of the head.

This is a worthwhile book which presents a difficult subject with very little lost motion. The type is clear and easy to read. The illustrations, as has been noted, are numerous and on the whole excellent. Both the author and publisher are to be congratulated.

F. G.

SOLVING SCHOOL HEALTH PROBLEMS. The Astoria Demonstration Study. By DOROTHY B. NYSWANDER, PH.D., Director of the Study. Pp. 377; several tables. New York: The Commonwealth Fund, 1942. Price, \$2.00.

PUBLIC school health programs have aroused dissatisfaction in recent years since the technique—medical and educational—of conducting health examinations has developed rapidly but the organization methods of supplying these to the public still rest in the Middle Ages. This report of Dr. Nyswander is really the culmination of a progressive series which started first with a survey of school health in about 90 cities of varying sizes, then a study of a sample of school children and their health and finally a survey of the methods used in detecting and correcting physical defects in New York City schools. The report then sets forth the applications of modern administrative methods to the great health problem in the public schools of a representative section of our largest city.

The study was sponsored by a variety of organizations such as the American Child Health Association, the Milbank Fund and the Metropolitan Life Insurance Company, etc., and carried out by a field staff with an advisory committee of physicians and public health experts. How to bring Public Health in all respects including its educational aid to a quarter of a million children, and indirectly to their parents, was the core of the problem—these children and parents springing from varying backgrounds of race, religion, intelligence, language and superstitions. How to develop up-to-date administrative and field methods of public health in schools in, around and through an inadequate system without disrupting too much the functioning program was the active problem. How skillfully, practically and how adequately this was done the reader can judge only by careful perusal of this report. An old method of screening out sick, undernourished and handicapped children was gradually eliminated and another coördinated and more practical substituted. Simplified record and "follow-up" systems were devised. Coöperation between teachers, parents, school physicians and private physicians was secured to the mutual advantage of all, and especially the children.

The book begins with a description of the school health program used in New York City in 1936 and a survey of the district selected for the study. Then there is a description of the school physician and his job, the usual findings of the school health examination, and follow-up of cases, the work of the teachers in a first-class program, the duties of the school nurse and finally a discussion of records and their availability.

Problems of visual testing, hearing, dental care, and the direction and management of children with cardiac diseases were skillfully posed and solved. The final stage of the study was devoted to the education of others in the methods, techniques and point of view developed during the earlier years of the Astoria District Study. Thus the whole city reaped the benefit of a localized demonstration in school health. The results: a more thorough physical examination of more children, elimination of long delays in securing correction of defects, avoidance of conflicts of professional opinion, increased interest in health problems of school children by officials and others in the city and finally the development of an up-to-date school health staff in New York City.

The aim of a school health service is not only the detection and correction of defects but also the development of a real concern for *positive* health and its relation to education. This demonstration has led the way in our country in public school health administration. Other valued items of interest in the volume are the descriptive charts of the record cases used, the classification of cardiac cases, and the exhibits, which are in the appendix.

E. T.

A SHORT HISTORY OF NAUTICAL MEDICINE. By LOUIS H. RODDIS, M.D., Captain, Medical Corps, United States Navy. Pp. 359; 12 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$3.00.

THOUGH secondary sources for nautical (maritime) medical history may be copious, as is indicated in a final bibliographic note in this volume, there seems to be no one place where even the high spots of the subject have been adequately collected in one volume. One, therefore, welcomes all the more this compact history, which includes the results of the author's studies of U. S. Naval Medicine. It is good to know also that his biographies of the Surgeon Generals of the U. S. Navy are already appearing in the *U. S. Navy Bulletin*.

The chapters cover nautical medicine of classical and medieval times, the diseases characteristic of the old sailing ships, naval medical departments, hygiene, hospitals, uniforms, the medicine of the merchant marine and nautical research.

Greek and Roman practices, James Lind and Scurvy, "Yellow Jack," Gilbert Beane and Thomas Trotter are among the topics considered. The chapter on U. S. Naval Medicine, which occupies a good quarter of the volume, selects Lewis Heerman, of Tripoli fame; Edward Cutbush, "The Nestor of the Medical Corps of the Navy" and author of the first American work on Naval Medicine; and W. P. C. Barton, First Chief of the Bureau of Medicine and Surgery for special notice. On page 250 are given the 10 chief contributions of the Medical Department of the U. S. N. to nautical medicine and on pages 351-4 a useful table of important chronologic events in naval medicine.

We welcome a book on this subject, especially at the present time and especially when it is as well and entertainingly done as is this volume by Captain Roddis.

E. K.

LEUKEMIA IN ANIMALS. By JULIUS ENGELBRETH-HOLM, M.D., Director of the Cancer Research Laboratory of the Danish Anti-Cancer League; Chief Pathologist of the Finsen Institute and Radium Station of Copenhagen. Pp. 245; 44 figures. Edinburgh: Oliver & Boyd, 1942. Price, 15/-n.

THIS well-written book might serve as a text to illustrate the multiplicity of methods used and their coördination by modern students of disease. The author points out that it was in 1858, 12 years after the recognition of human leukemia by Virchow, that Leisering reported the first case of leukemia in an animal—the horse. The first transmission experiments were attempted in 1872, but were unsuccessful until 1908, when Ellermann and Bang transmitted leukemia from diseased to healthy fowls.

The spontaneous leukemias in birds and mammals are treated separately, then their experimental production as well as numerous transmission experiments are considered. The hereditary factors, which have been so successfully investigated by Americans, are dealt with in detail. The author believes that leukemia is a neoplasm, and what he says of its occurrence in fowls might well serve as a general conclusion: "In spite of much consideration, in spite of the study of a great amount of material, in spite of numerous observations of the occurrence of the disease in different regions and under varying conditions, the etiology of leukemia is still very nearly as obscure as ever."

H. S.

PSYCHOSURGERY. By WALTER FREEMAN, M.D., Ph.D., F.A.C.P., and JAMES W. WATTS, B.S., M.D., F.A.C.S. Pp. 337; 81 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.00.

THIS is the only monograph in English upon the value of surgery in the treatment of certain types of mental disease. The history of the develop-

ment of psychosurgery is outlined from the early efforts of Burchhardt and Puusepp to the more important and impressive results obtained by Moniz. The first bits of clinical evidence of the effect of injury to the frontal lobes upon personality, such as the crow-bar skull, are carefully considered. Based upon these facts as well as upon the carefully studied cases of deliberate bifrontal lobectomy for the removal of brain tumors, a case is made for section of the prefrontal association pathways in the treatment of certain types of mental disease. Eighty carefully studied cases form the basis of this monograph. The preoperative care, the operative technique and post-operative sequelæ are carefully considered. Especially interesting is the description given of the patients' reactions in the operating room as the last of the four frontal quadrants is sectioned.

In the selection of cases for this procedure the best results were obtained in the involutional depressions and the obsessive tension states. The schizophrenics were less frequently benefited. Three operative deaths occurred in this series.

Whether or not the use of surgery in the treatment of mental disease has any appeal, this book should be thoroughly studied. The cases are described clearly and in detail. The facts are presented impersonally and without bias. There is a noticeable lack of special pleading or an effort to suggest that any panacea has been found. The authors simply detail certain facts about a relatively new—and, to many psychiatrists—radical treatment of mental disease.

But they do more than simply this. A definite step forward has been made in unraveling the psychophysiology of the frontal lobes. Whether or not the conclusions drawn on these points are correct, it must be admitted that, looked at solely as a bit of pure research and regardless of any benefit to the patients, important facts with regard to the functions of the frontal lobe have been discovered.

The format of the book is excellent; the print clear; the illustrations more than adequate. Every psychiatrist should read it if only for the purpose of developing arguments against the use of surgery in mental disease.

F. G.

PAIN. BY SIR THOMAS LEWIS, M.D., F.R.S., Physician in Charge of Department of Clinical Research, University College Hospital, London: Fellow of University College, London. Pp. 192; 27 figures. New York: The Macmillan Company, 1942. Price, \$3.00.

This monograph is a review of the author's experimental work on pain, correlated with pertinent experiments of other investigators. Thus a well-rounded picture is obtained of the present status of the subject up to the time when the author's work was interrupted by war. The early chapters furnish the anatomic background, stating in detail which parts of the body may give rise to pain and which may not. The quality of pain is then analyzed. It appears that the popular concept of pain as being pricking, stinging, burning, etc., is ill-founded; that the quality of pain depends not on the stimulus but on the tissue and that from the standpoint of pain there are only two kinds of tissues, the superficial and the deep.

Superficial tissues comprise the skin and certain mucous membranes; deep tissues are what the term implies, and in addition, the glans penis and nasal mucosa. Corresponding to the two types of tissue we have two types of pain and two only, which are qualitatively different. These may be exemplified by pricking the skin (superficial pain) and by squeezing the finger web (deep pain).

The factors concerned in the pain of inflamed skin are discussed, though in less detail than the Reviewer would have wished. Head's division of

sensation into protopathic and epicritic is found not to be supported by more recent observations, and to be no longer useful as a hypothesis.

The latter part of the book is concerned largely with referred pain, which is a subject too large for summary in this review. I will merely state the author's opinion on how impulses arising from viscera, *e. g.*, the heart, are referred to the distribution of somatic nerves of the same segment. Such reference, he believed, is due not to diffusion of impulses through the gray matter of the spinal cord, as postulated by Sturge, but rather take place in the sensorium. The viscera are represented in the sensorium only in mass and not in detail. Impulses received from such areas are referred by the sensorium to regions well represented in detail, that is, the somatic regions. The present work deals with pain in general rather than with pain of individual organs. And the general reader may be warned that this is not an easy book to read and comprehend. M. M.

MEDICAL MANUAL OF CHEMICAL WARFARE. [Anonymous.] Reprinted by permission of The Controller of His Britannic Majesty's Stationery Office. Pp. 121; 10 plates, several tables. Revised Edition. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1942. Price, \$2.50.

THIS manual, prepared by the British for the use of medical officers in wartime, and now reprinted in the United States, gives in concise form descriptions of the various gases used in warfare, the effects that they produce, and the methods to be used in treatment.

Gases are divided, as usual, into Vesicants, Lethal, Harassing and Accidental varieties. Of the vesicants, in fact of all the gases, Mustard Gas is still regarded as the most important and is given corresponding space. Its systemic effects are understated, however, and as usual, its toxic effect on the bone marrow has been overlooked.

The illustrations have been reproduced so badly that they would much better have been omitted. Considering the size and price of the book, one might have expected a much better job, though it is still a useful, practical compend. E. K.

NEPHRITIS. By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 344; 120 illustrations. New York: Grune & Stratton, Inc., 1942. Price, \$5.50.

THERE is perhaps no branch of medicine in which our knowledge is increasing as rapidly as in Bright's disease. A new monograph on this subject is scarcely justified unless it presents the results of modern work fully and clearly. This the present work does not do. For example, the mechanisms of albuminuria and hypertension are explained neither fully nor clearly from the modern viewpoint. The author appears to dislike the clearance tests. Probably the most valuable part of the book is 25 case reports in tabular form showing the effects on volume and specific gravity of the urine and on blood chemistry produced by administration successively of water, 750 cc. NaCl, 10 gm., and urea, 20 gm. The subjects covered are glomerulonephritis and nephrosis, but not nephrosclerosis. M. M.

ANNUAL REVIEW OF PHYSIOLOGY. By JAMES MURRAY LUCK, Editor, Stanford University, Volume IV, 709 pages. Stanford University, Calif.: American Physiological Society and Annual Reviews, Inc., 1942. Price, \$5.00.

THE purpose, nature, character, and scope of the Annual Review of Physiology is now well known. The reviews of the subjects presented in

this volume maintain the high standard set in previous years. The subjects and authors of the reviews are as follows: Permeability—Blinks; Physiological Effects of Neutron Rays—Aebersold and Lawrence; Physiological Aspects of Genetics—Strandkov; Developmental Physiology—Hamilton and Willier; Water Metabolism—Peters; Growth—Avery; Energy Metabolism—Chambers, Shorr and Barker; Physiology of the Skin—Baird, Lever, and Spies; Peripheral Circulation—Hertzman; Heart—Visscher; Blood—Smith; Digestive System—Van Lieve; Kidney—Shannon; Electrophysiology—Gerard; Spinal Cord and Reflex Action—Ruch; Central Nervous System—Hines; Autonomic Nervous System—Hare and Hinsey; Sense Organs—Hartline; Metabolic Functions of Endocrine Glands—Long; Physiology of Reproduction—Hisaw and Astwood; Physiological Psychology—Richter; Applied Physiology—Behnke and Stephenson; Pharmacology of Drug Addiction—Smith. S. G.

THE RETINA. The Anatomy and the Histology of the Retina in Man, Ape and Monkey, including the Consideration of Visual Functions, the History of Physiological Optics, and the Histological Laboratory Technique. By S. L. POLYAK, M.D. Pp. 607; 100 illustrations (1 in color). A fiftieth anniversary publication of the University of Chicago Press, Chicago, 1941. Price, \$10.00.

IMPORTANT information on the retina, scattered in journals, books and even in ancient manuscripts, has been diligently collected and presented by the author in a one volume monograph. In addition, he includes the results of his own investigations on the retina and supplements his historical and morphologic survey with a discussion on the physiologic problem of this complex organ. A large number of figures and an up-to-date bibliography make the book complete. The reader will be greatly satisfied, having in his hands a book written by a scholar who is master of his subject. This monograph is one of the most valuable contributions of recent years in the field of medical literature. G. DER.

EDITH CAVELL. By HELEN JUDSON. Pp. 288; frontispiece of Edith Cavell. New York: The Macmillan Company, 1941. Price, \$2.50.

THE story of Edith Cavell, a supreme example of the German inability to comprehend the reactions of enemy minds, regains the poignant interest that it held over the emotions of those engaged in the first World War. The author, who was able to interview Miss Cavell's friends and relatives, visit the scenes of her activities and study her unpublished letters and the complete German dossier of the trial, gives a satisfying picture of this unique life of devotion to humanity, as such, culminating in her final famous remark to the Rev. Mr. Gahan in prison: "Patriotism is not enough; I must have no hatred nor bitterness to anyone." It was in this sense that when Nationalism was rampant Shars classed her as "heretic" and it was this in turn that led the author to explain and set forth Miss Cavell's true personality.

Those medically minded will find a further interest in the effect of heredity on her puritanical sense of duty combined with kindness and practical help to the unfortunate, and in her achievement in raising the nursing profession in Belgium to new standards and efficiencies.

Though one may disagree with the author as to the illegality of the execution according to the German code (was she guilty of "conducting soldiers (mannschaften) to the enemy,") the reasons offered for selecting for execution the only English subject and one Belgian out of all those convicted seem cogent. For different reasons, this nurse stands with Florence Nightingale as the chief glories of the nursing profession. E. K.

NUTRITIONAL DEFICIENCIES. DIAGNOSIS AND TREATMENT. By JOHN B. YOUMANS, A.B., M.S., M.D., Association Professor of Medicine and Director of Post-Graduate Instruction, Vanderbilt University Medical School, Nashville; assisted by E. WHITE PATTON, M.D. Pp. 385; 14 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$5.00.

THE announced purpose of this volume is to glean from the great mass of the literature the information most helpful to the practising physicians to "a proper understanding and management of the nutritional deficiencies" The vitaminoses naturally occupy the greater part of the book, but deficiencies of iron, iodine and protein are also included, together with brief mention of the rôle of the "trace" metals, kind of the essential fatty acids in nutrition.

An appendix contains the factual material summarized in tabular form, tables indicating the "excellent" and the "good" sources of the food factors, and detailed descriptions of accepted methods for diagnosing each deficiency (*e. g.*, the use of the Cowgill chart or the Williams and Spies formula for determining the adequacy of the vitamin intake). A useful index is included. E. W.

ESSENTIALS OF PATHOLOGY. By LAWRENCE W. SMITH, M.D., Professor of Pathology, Temple University School of Medicine, and EDWIN S. GAULT, M.D., Associate Professor of Pathology, Temple University School of Medicine. Foreword by JAMES EWING, M.D., of the Memorial Hospital, New York City. Second Edition. Pp. 960; 685 illustrations, 140 plates, many in color. New York: D. Appleton-Century Company, Inc., 1942. Price, \$10.00.

PURSuing their original ideal of a practical, concise, up-to-date text which eliminates confusing details and imprints vividly upon the minds of medical students only the fundamental facts of pathology, the authors have retained the illustrative and repetitive feature of case histories and abundant pictorial material, sacrificing minutiae for brevity. The section on the fundamental pathologic processes has been enlarged and amplified to include pathologic physiology and some modern theories, the case histories have been shortened, and a bibliography has been added. As in the first edition, emphasis is placed upon such currently important problems as neoplasms, parasitic infestations, and oral and respiratory diseases, with perhaps too little on such older favorites as syphilis, and central nervous system tumors.

Supplemented by complete lectures and demonstrations, the volume should be adequate, perhaps ideal, for basic reading, but cannot be used as a reference handbook. M. F.

THE PATHOLOGY OF TRAUMA. By ALAN RICHARDS MORITZ, M.D., Professor of Legal Medicine, Harvard Medical School; Lecturer in Legal Medicine, Tufts College Medical School; Pathologist, Massachusetts State Dept. of Public Safety. Pp. 386; 117 illustrations. Philadelphia: Lea & Febiger, 1942. Price, \$6.00.

THE first part of this book deals with general considerations of the relation of trauma to infection, trauma and tumors, types of injurious agents, and general tissue reactions to injury. Then the gross and microscopic pathology of each organ is dealt with separately. In addition to anatomic changes, many functional disorders are discussed, such as shock, neurogenic disturbances of the cardiovascular system, post-traumatic

neurogenic disturbances of the bladder, sequence of functional changes in asphyxia.

There are descriptions of the changes resulting from detonations of explosives, but the emphasis is not upon the effects of modern warfare but rather upon the traumatic injuries encountered by any pathologist, with quite detailed information useful in medicolegal cases of violent deaths and settlements for compensation for accidents.

The book is full of interesting and unusual observations, accurate details, and has many excellent photographs. The author writes critically and expresses sound judgment, and an unbiased point of view when presenting controversial matters. I. Z.

NEW BOOKS

Edinburgh Post-Graduate Lectures in Medicine. Vol. 2 (1940-41). Pp. 540; several figures. London, Eng.: Oliver & Boyd, 1942. Price, 12/6 net.

Pulmonary Tuberculosis and Its Treatment. By HANS JACOB USTVEDT, M.D. (OSLO), First Assistant Physician to the State Hospital, Oslo; Formerly First Assistant Physician to the Ullevaal Municipal Hospital, Oslo. Translated by A. L. JACOBS, M.R.C.P. With a Foreword by W. D. W. BROOKS, D.M. (OXON), F.R.C.P. Pp. 252; 45 figures. London, Eng.: John Bale & Staples, Ltd., 1942. Price, 25/-.

The Modern Treatment of Venereal Diseases. By E. T. BURKE, D.S.P., M.B., CH.B. (GLAS.), Lieut.-Col. (late) Royal Army Medical Corps; Formerly Director of the London County Council (Whitechapel) Clinic; Consul and Venereologist in the Public Health Department of the London County Council; Lecturer in Venereal Diseases in the London Hospital Medical College, Univ. of London; Member of the Sub-Committee on Antisyphilitic Remedies of the Therapeutic Trials Committee, Medical Research Council; Assistant Editor, "British Journal of Venereal Diseases." Pp. 105, many tables. London, Eng.: John Bale & Staples, Ltd., 1942. Price, 12/6d.

Synopsis of Pathology. By W. A. D. ANDERSON, M.A., M.D., Assistant Professor of Pathology, St. Louis University School of Medicine; Pathologist, St. Mary's Group of Hospitals. Pp. 661; 294 illustrations, 17 color plates. St. Louis, C. V. Mosby Company, 1942. Price, \$6.00.

This volume is intended to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks and reference works. By the presentation of pathology in a compact and condensed form, it is designed to be useful to the medical student, to the dental student studying general pathology, and to the clinician who must maintain familiarity with the foundation sciences of medical practice . . . The objectives of the volume preclude bibliographic reference to many authors whose works have been consulted, although indebtedness to them is acknowledged. The references which have been included were chosen because they are reviews, or refer to subjects in which there has been recent interest or advance in knowledge. This volume partakes of many merits and limitations of works of its kind. E. K.

Microbiology and Man. By JORGEN BIRKELAND, PH.D., Assistant Professor in Bacteriology, Ohio State University. Pp. 478; 35 figures. Baltimore: Williams & Wilkins Company, 1942. Price, \$4.00.

The Pleuro-subpleural Zone. By J. SKLADAL, Reader in General and Experimental Pathology, Caroline University, Prague; Head of the Chest Department, Bulovka Hospital, of the City of Prague; Consulting Physician, the Masary, Institute for Treatment of Lupus, Prague-Motol. Pp. 103; 11 plates. Cambridge: The University Press; New York: The Macmillan Company, 1942. Price, \$275k.

Fluorine and Mental Health. Edited by FOREST RAY MOULTON. Publication of the American Association for the Advancement of Science, No. 19. Smithsonian Institute Bldg., Washington, D. C. Publication Committee, H. TRENDLEY DEAN, PAUL C. KITCHIN. Pp. 101; many figures and charts. 1942. Price, \$3.00.

NEW EDITIONS

National Formulary. Prepared by the Committee on National Formulary by authority of the American Pharmaceutical Association. Official from November 1, 1942. Seventh Edition. Pp. 690. Washington, D. C.: American Pharmaceutical Association, 1942. Price, \$6.00.

Conforming with the new practice of the U. S. Pharmacopœia, this revision has been made 5 instead of 10 years after the previous one and becomes official on Nov. 1, 1942. Although it is still primarily a book for the pharmaceutical rather than the medical profession, N.F. VII contains a new chapter on ingredients of reagents and preparations for use in the clinical laboratory, including a summary of the chemical and physical properties of the various substances involved, which should make the book distinctly useful to workers in clinical laboratories. As compared with N.F. VI, this edition contains 97 new items, 71 of which were official in the last (XI) revision of the U.S. Pharmacopœia but are not included in the forthcoming XII revision; in this list are such things as vinegar of Squill, Cantharis, Creosote, Dichloramine T, Guaiacol, Iodoform, Kino, Dover's Powder, Santonin, Syrup of Ferrous Iodid, Tincture of Ferric Chloride, Tincture of Veratrum Viride, and Trional. Thus is retained the traditional status of the N.F. as an official repository for drug preparations that are declining in popularity but are still rather widely used.

C. S.

Stedman's Practical Medical Dictionary. By STANLEY THOMAS GARBER, B.S., M.D., University of Cincinnati, College of Medicine. Fifteenth Edition, revised, with Etymologic and Orthographic Rules. Pp. 1257. Baltimore: Williams & Wilkins Company, 1942. Price, with Thumb Index, \$7.50; without index, \$7.00.

This new edition, after 3 years, the first to appear under the sole authorship of the late Dr. Stedman's nephew, worthily maintains the high standard and tradition of its predecessors. This edition has been completely reset, has 45 fewer pages than the 13th edition and is slightly smaller. The changed type is less pleasant to the eye, but probably saves searching time. As one would expect, hundreds of new titles are included and many that have become obsolete have been omitted. The latest variations in bacterial terminology (see Bergey's Manual, 1939) have been included, so that one should now master 500 new species, new genera, families and even a new order—"Canlobacterioles," as well as new names for old acquaintances. Fortunately, chemical synthetics are not offered in the same detail!

E. K.

The Care of the Aged (Geriatrics). By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Department of Public Health. Fourth Edition. Pp. 589; 50 illustrations. St. Louis, C. V. Mosby Company, 1942. Price, \$7.00.

Gray's Anatomy. By HENRY GRAY, F.R.S.; Late Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Edited by WARREN H. LEWIS, B.S., M.D., Member, the Wistar Institute of Anatomy and Biology, Philadelphia. Twenty-fourth Edition. Pp. 1428; 1258 figures, mostly in colors. Philadelphia: Lea & Febiger, 1942. Price, \$12.00.

Starling's Principles of Human Physiology. Edited and Revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. (BIRMINGHAM), Jodrell Professor of Physiology in University College, London. Chapters on the Special Senses Revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S.; Professor of Physiology at St. Bartholomew's Medical College. Eighth Edition. Pp. 1257; 673 figures. Philadelphia: Lea & Febiger, 1942. Price, \$10.00.

PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE TREATMENT OF MÉNIÈRE'S SYNDROME

It was early in the course of our own Civil War, in 1861, to be exact, that Ménière^{8a} described a group of symptoms which he thought constituted a separate disease entity. His description of the symptomatology of the disease which bears his name is a classic, and little has been added through the years. Ménière's syndrome is common, affects people in the middle years of life, and shows a characteristic triad of symptoms: vertigo, tinnitus and deafness. The etiology is unknown; its pathology is still a subject for investigation and some degree of speculation. The treatment of Ménière's syndrome remains a varied one.

At the present time the most effective treatment of Ménière's syndrome may be divided into two categories: medical and surgical. According to Grove,⁷ surgical intervention should be reserved for those patients who have not responded to a medical régime, to those patients who for economic or other reasons cannot be kept on a medical régime, and for those patients whose occupations are such as to preclude the possibility of any return of the vertigo because of carelessness in following a medical régime. Of the surgical measures proposed, it seems to Grove that total section of the acoustic nerve is indicated for those whose hearing in the affected ear has fallen below a usable level and that the differential section of the vestibular portion of the nerve is the operation of choice for those with usable hearing. These operations should not prove hazardous in the hands of the competent neurosurgeon. Dandy⁵ maintains that Ménière's syndrome can be permanently cured by division of the auditory nerve. The procedure carries almost no risk to life. When there is reason to save remaining hearing, partial division of the nerve is done. The vestibular branch can be

divided, leaving a part of the auditory branch intact. Generally, three-fourths of the anterior part of the auditory nerve is sectioned to insure total elimination of the vestibular fibers. Division of three-fourths of the auditory branch of the nerve does not affect hearing, apparently because of redundant fibers carrying similar functions. If there is a division of one auditory nerve, or only its vestibular portion, no permanent loss of vestibular function ensues. Immediately following operation the patient may or may not have transient attacks of dizziness not unlike an attack of Ménière's syndrome. Gradually, however, it decreases and then disappears. Only occasionally will it persist for a long period of time. Tinnitus, too, may or may not disappear following section of the nerve; if it persists it may or may not improve, but in about 50% of cases it disappears completely. Section of the entire eighth nerve or its vestibular portion usually eliminates the violent attacks of vertigo, but that it does not always do so is indicated by Walsh and Adson¹⁴ who state that of 20 patients who had a section of either the whole nerve or its vestibular portion, 15 were able to resume their work, and of the remaining 5, 3 were highly nervous women. They suggest that in those cases which do not gain relief from the total nerve section the condition is bilateral and the opposite vestibular nerve should be sectioned, but in the majority of cases the vertigo, if not completely eliminated, is improved to the extent that the individuals can resume their occupations. Mollison⁹ exposes the prominence of the external semicircular canal by a simple mastoid operation and injects a few drops of absolute alcohol into the membranous canal after removal of its bony covering. He reports that 74% of patients operated upon considered themselves cured, 10% as not benefited, and 16% lost track of. Berggren³ employs the same method of alcohol injection but through another approach. He makes a flap of the entire posterior one-half of the membrana tympani, turns it upward and forward, and after scarifying the mucous membrane over the promontory he perforates the bone in this region with a dental burr. Putnam¹² suggests drilling into the superior canal with a burr through a subtemporal approach and then destroying the labyrinth by coagulation.

As a result of their experiments, observations and therapeutic results, Mygind and Dederding¹¹ conclude that in Ménière's syndrome there is a disturbance of water metabolism not only in the ear but also, with individually varying location, in greater or smaller parts of the entire organism. These disturbances have a tendency to periodic fluctuation caused by a series of external and internal factors which seem to exert their action essentially through a partly local, partly general, vasomotor—especially capillariomotor—dysfunction. In the past their treatment consisted of a restricted fluid intake of about 700 cc. daily and sometimes even as low as 350 to 400 cc., a diet low in salt for the purpose of increasing diuresis, a reduction diet for patients who were overweight, together with exercise, massage and light therapy to stimulate vasomotor tone. Furstenberg, Lashmet and Lathrop⁶ disagree with the deductions of Mygind and Dederding, namely that water retention is the cause of the Ménière syndrome and when the body accumulates water that sodium is also stored, and direct their treatment to a reduction of the body sodium. They maintain that

the retention of water and sodium will produce an attack; but loss of water and sodium does not produce an attack. The retention of water without sodium will not produce an attack, while the loss of water with a retention of sodium will produce an attack. Furstenberg therefore places his patients on a salt-free diet to limit the intake of sodium, and on ammonium chloride to encourage an increased excretion of sodium while permitting the patients all the water desired. He states that the water intake need not be considered if the concentration of the sodium ion in the body is kept at a low level. Brown⁴ and Bartels² have reported favorable results with this régime. Walsh and Adson¹⁴ report a series of 186 cases of which 152 were treated with a low salt diet with or without the addition of medication for salt elimination. They employed potassium nitrate instead of ammonium chloride and found it to be as efficacious. Of the 152 patients treated with a low salt diet with or without the addition of sodium-eliminating medication they found 34% experienced complete relief of the vertigo, 28% experienced variable degrees of improvement, and 38% experienced no relief whatever. Morsch¹⁰ treated 4 patients with Ménière's syndrome who also had symptoms of avitaminosis for vitamins A and C. He reports an improvement in the vertigo, tinnitus and deafness after intensive vitamin treatment.

In 1940 Shelden and Horton¹³ advocated the use of histamine in all cases of Ménière's syndrome without exception and claimed immediately satisfactory results in a large proportion of cases. They reject the views which place pathologic changes in Ménière's syndrome in various cerebral structures and believe that the lesion is situated in the inner ear, that it consists essentially of localized alteration in permeability of the capillary wall and that this causes regional edema. The labyrinth is held to be the specific site most frequently involved, and tinnitus and diminution of hearing is considered evidence of secondary cochlear involvement. Four of 15 patients were treated by the subcutaneous route and 11 intravenously. The patients in the latter group were given intravenously from 1 to 3 doses of 1.9 mg. histamine acid phosphate dissolved in 250 cc. normal physiologic salt solution. The time for each administration was approximately $1\frac{1}{2}$ hours. Spectacular results were reported in all 15 patients, and no ill-effects were noted following the use of histamine. For the prevention of future attacks, Horton finds that an adequate maintenance dose is usually 0.1 to 0.2 mg. histamine given subcutaneously 2 to 4 times a week. In commenting on the work of Shelden and Horton, Woltman¹⁵ states that because of its value and ready applicability he does not believe that the treatment proposed by Furstenberg will be supplanted by the histamine treatment, but that the latter is of great value when vertigo and vomiting are extreme.

To Atkinson¹ it seems not unjust to conclude from the evidence he has found that histamine is not suitable for universal application in cases of Ménière's syndrome. It is suitable for selected cases only, and only by assigning individual cases to their correct group can effective treatment be assured. It is on a par with typing pneumonia cases for serum treatment. Confusion has crept in—his mail is ample evidence of it and the precipitating cause for his paper—because histamine has two effects, an immediate and a remote, and the two have not been

distinguished. The immediate effect is vasodilator, in consequence of which it often gives immediate and sometimes dramatic relief from a vasoconstrictor attack, though no more immediate or dramatic than other peripheral vasodilators. Its remote effect, by inducing a resistance to its action in the body in the same way in which a vaccine produces a resistance to the effects of a microorganism, is *nil* or actually even vasoconstrictor. For this reason its repeated administration, while exceedingly effective in the vasodilator group as a desensitizing agent, in vasoconstrictor cases not only fails, after the initial doses, to produce the desired effect but sometimes even makes matters worse. Histamine will not relieve all, or even most, cases of Ménière's syndrome. Preliminary accurate grouping is essential to success.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF
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PHOTODYNAMIC EFFECTS IN DERMATOLOGY

PART II

THIS paper is a continuation of a review in the previous volume (*Am. J. Med. Sci.*, 203, 608, 1942) on Photodynamic Effects in Dermatology, in which we propose to discuss the diseases with a prominent cutaneous aspect in which photodynamic effects appear to play a leading part. Because of the voluminous material, the discussion will be limited to diseases in humans, and only some of the more important diseases will be discussed in detail. In addition, some mention will be made of prevention and treatment of the local cutaneous reaction to light.

The effects of light on the abnormal or morbidly reacting skin of human beings has been known for about 150 years. Rasch¹⁵⁵ has sum-

marized the important contributions dealing with the development of knowledge concerning the diseases of the skin which are caused, in part, at least, by light. The first to describe one of the diseases produced by the sun was Willan,²⁰⁶ in 1798. He called the condition *eczema solare*, but Rasch believes Willan's disease to be similar to the *eczema-like polymorphic light eruption* later described by himself.

In 1835 Rayer¹⁵⁶ described a patient with vesicular and papular lesions on the hands and back produced by light, and in 1860 Bazin⁹ described *hydroa vacciniforme*. Kaposi⁹⁹ (1870) described *xeroderma pigmentosum* but was not aware of the relationship of this disease to light (Unna,¹⁹¹ 1894). Other conditions were subsequently described: J. Hutchinson⁸⁹ (1878), *prurigo æstivalis*; Veiel²⁰⁰ (1887), *eczema solare*. In 1906 and 1907 Dubreuilh^{41c} stated that most of the *epitheliomata* of the face and so-called senile alterations of the skin were produced by the light's rays.

As is the case even today, confusion has marked the clinical differentiation of these various dermatoses. The early attempts to classify them were largely clinical and the only evidence that light was a causative factor was the fact that the eruptions were limited to the exposed parts, and that the patient gave a history of exposure to sunlight just before the attack. Rarely was there an attempt to reproduce the lesions by exposure. Further stimulation to study of these diseases was the discovery of porphyrin by McCall Anderson³ (1898) in the urine of 2 patients with *hydroa*. Subsequent demonstration of photodynamic action and a possible allergic mechanism to explain abnormal sensitivity to light have been discussed in the first part of this review.

That animals have diseases due to photosensitivity has likewise been known for over 150 years and the various diseases have stimulated considerable research. The reader is referred for complete discussions of the photodynamic diseases in animals to Mathews^{125a,b,c} and Blum.^{19a,b}

Blum^{19a,b} has formulated simple requirements comparable to the laws of Koch in microorganismal diseases, before a given condition may be attributed with certainty to photodynamic action:

1. The symptoms of light sensitivity must be elicited by exposure of the animals to sunlight, preferably to sunlight through window glass.
2. A photodynamic substance must be isolated in pure form, which will produce the symptoms if injected into the experimental animals only when followed by exposure to light.
3. It must be demonstrated that the wave-lengths which produce the sensitivity in postulates (1) and (2) are identical. The study of the absorption spectrum of the photosensitizing substance isolated in the development of postulate (2) should be of assistance in establishing postulate (3), since the action spectrum for the production of the symptoms of photosensitivity should resemble the absorption spectrum of the substance.

These requirements are not necessarily fulfilled in all diseases usually attributed to light, but nevertheless they offer a guide for future study. While they were apparently proposed for diseases in animals, they apply with equal force to man.

Numerous classifications of diseases, either produced or affected by light, have been proposed. Blum's^{19b} attempt to develop a simple general classification is a step in the right direction, particularly from the experimental standpoint. His classification is as follows:

A. Skin lesions produced only by radiation which induces the sunburn of normal skin (wave-lengths shorter than 3300 Å). (Polymorphic light eruption; skin cancer; xeroderma pigmentosum.)

B. Skin lesions due to abnormal photosensitizing substances in the skin. (Urticaria solare.)

We have adopted that of Hausmann and Haxthausen⁷⁵ (1929), not because it is necessarily the most exact, but because it is clinical. The Hausmann and Haxthausen classification is as follows:

- I. The action of light on pathologically light-sensitive skin.
 - A. *Hydroa aestivale*.
 1. *Hydroa aestivale* with congenital porphyria.
 2. *Hydroa aestivale* with chronic porphyria.
 3. *Hydroa aestivale* without porphyria.
 - B. Chronic polymorphic light eruption.
 - C. Pellagra.
 - D. So-called pellagroid eruption due to light.
 - E. Unclassified eruptions due to light, accompanying metabolic and other internal disturbance.
 - F. Sensitization of the skin to light by medicaments.
 1. Exogenous.
 2. Endogenous.
 - G. Xeroderma pigmentosum.
 - H. Late xeroderma pigmentosum, Seemanshaut, other photogenic forms of skin cancer.
 - I. Degeneration of elastic and collagen tissues of the skin.
 - J. Photoelectric dermatitis.
- II. Skin diseases exacerbated or precipitated by light.
 - A. Action of light on acute exanthemic infections.
 1. Variola.
 2. Other acute exanthemata.
 - B. Intrinsic skin diseases.
 1. Acne vulgaris.
 2. Eczema.
 3. Multiform exudative erythema.
 4. Lupus erythematosus.
 5. Pityriasis streptogenes faciei.
 6. Psoriasis.
 7. Rosacea.
 8. Toxic exanthemata.
 9. Urticaria.
 10. Other skin diseases.

Many review studies have appeared from time to time dealing with the various dermatoses produced by light. Among them are those of Rasch,¹⁵⁵ Greenbaum,^{68a} Anderson and Ayres,² Bechet,^{11a} Mercer,¹²⁸ S. Epstein,⁴⁸ Hübner,⁸⁸ Lampe,¹¹² and especially the monograph of Blum.^{19a} Special studies devoted to individual phases of this problem will be mentioned in appropriate places.

Hydroa Vacciniforme seu Æstivale. Since Bazin⁹ (1860) first described hydroa vacciniforme there have been several designations for this disease or variations of it, leading to much confusion. Rasch¹⁵⁵ believed that the name *hydroa vacciniforme* had been applied to two different diseases, that described by Bazin, the typical form resulting in cicatrix; and the other, consisting of a special symptom complex composed of porphyria, the outbreak of large pemphigus-like blebs on the face, ears, and hands, which lead to gangrene and a great loss of substance, and was first attributed to the action of light by McCall Anderson.³ Prurigo æstivale is also confused with hydroa vacciniforme. Epstein⁴⁸ has shown that Pick's¹⁴⁷ differential criteria for prurigo

æstivale are all subject to exception, making the absolute differential diagnosis impossible. In addition, the occurrence of porphyrinuria and mutilating dermatoses of the exposed parts have led a number of authorities to discuss the porphyrias as part of the same picture. Because hydroa is not associated with all cases of chronic or congenital porphyria and because porphyrinuria does not occur in many of the cases of hydroa, we are discussing the two subjects separately.

Clinically, hydroa vacciniiforme seu *æstivale* consists of an eruption of variously sized bullæ appearing early in life, gradually subsiding after puberty, usually distributed on the exposed parts. In the majority of the cases scarring occurs with resultant severe disfigurement of the nose, ears and fingers. In certain abortive cases, scarring may be absent. In others the scarring may be so extensive as to resemble scleroderma. Hypertrichosis, ~~hyperpigmentation~~ and excessive sensitivity to trauma (epidermol) may be present. Porphyrinuria may be associated with the cutaneous lesions and occasionally alterations in the liver and spleen may also be noted.¹⁹³ Keratitis has also been observed. The teeth may be discolored by porphyrin. In some cases there may be an hereditary factor.

As in many phases of the problem of light-sensitive dermatoses, Blum and his associates^{19a, 21, 23} have been instrumental in furthering our understanding of hydroa vacciniiforme. Because of the occurrence of porphyrinuria in certain cases of hydroa vacciniiforme it was felt that this substance might be the photosensitizing agent involved in the production of such lesions. If hydroa lesions are the result of such action, they should be reproduced by the same wave-lengths as those to which porphyrins sensitize the skin. If porphyrin really were the sensitizing substance, Blum and Pace²³ thought it should be "possible to produce the lesions of hydroa by subjecting the skin to any wave-lengths between the lower limit of sunlight (about 2900 Å) and about 6500 Å, provided the intensity and time of exposure were great enough; but the greatest sensitivity should lie between about 3000 Å and 4500 Å." Blum and his associates, in common with many other investigators attempted to reproduce the lesions experimentally. The results of these studies were varied and inconclusive. They failed to demonstrate that the lesions of this disease are produced by the wave-lengths to which porphyrins sensitize the skin. They also found that repeated exposure to radiations which elicit sunburn in normal skin failed to reproduce the hydroa lesions.

Porphyrias. There is a group of congenital disturbances of unknown etiology characterized by a disturbed metabolism of the pyrroles and associated with the excretion of large amounts of porphyrins. Porphyria is to be distinguished from porphyrinuria, which refers merely to the excretion of abnormally great amounts of porphyrins in the urine. Günther⁷¹ classified the various clinical subgroups in this concept as modified by Waldenström,²⁰¹ into congenital, acute, and chronic types.

Recent contributors to the study of these conditions are Mathews,^{125a} Turner and Obermayer,¹⁹⁰ Turner,^{189a} Dobriner and Rhoads,³⁷ Schwartz and Watson,¹⁷¹ Nesbitt and Watkins,¹³⁶ and Hoagland.⁸³ Most of these studies are fully documented and bring the subject thoroughly up to date.

Congenital porphyria is attended with great sensitivity to light and the excretion of large amounts of Type I porphyrins. This type of porphyria was recently reviewed by Turner and Obermayer¹⁹⁰ who discussed 86 cases, 9 of which were considered doubtful. Dobriner and Rhoads³⁷ summarized the clinical manifestations as "(1) The excretion of large amounts of porphyrin; (2) discoloration of the teeth and bones by impregnation with uroporphyrin I; (3) sensitivity of the skin to light in the spring and summer, a symptom which often appears first in childhood. Blistering of the exposed areas of the face and extremities is observed, and the lesions heal with scar formation followed in many cases by deformity of the affected tissue." Turner and Obermayer point out, however, that hydroa vacciniforme is not the only dermatosis associated with porphyria, since approximately 14 cases of epidermolysis bullosa and other dermatoses have been less rarely reported in this connection. In some instances porphyrins have also been absent. Turner and Obermayer cited other less common concomitant findings in their review, including lesions in the eyes, the thyroid, the liver, the spleen, and the blood (anemia). Schreus and Carrié¹⁷⁰ record that porphyrin was found in the blister fluid. The urine in congenital porphyria is usually burgundy red with a brown tinge (varies from pale pink to almost black) and contains large amounts of coproporphyrin Type I and uroporphyrin Type I. The feces may contain an abnormally large amount of coproporphyrin.

Turner and Obermayer were unable to reproduce experimentally the eruption typical of porphyria in their patient, but note that their failure was one of a long series. They hypothesize that "in view of the existence of hydroa, epidermolysis bullosa and porphyria as independent clinical entities, and in consideration of the familial occurrence of each, it is suggested that each is a genetically different disease. The frequent coexistence of porphyria and a cutaneous disease may depend on some spatial or chemical relationships of the genes determining these conditions."

Acute Porphyria. Acute porphyria has been studied especially recently by Mason, Courville and Ziskind,¹²³ Waldenström,²⁰¹ Dobriner and Rhoads,³⁷ Turner,^{189a} Schwartz and Watson,¹⁷¹ Nesbitt and Watkins,¹³⁶ and Hoagland.⁸³ Acute porphyria has been subdivided into toxic and idiopathic varieties, but Nesbitt and Watkins¹³⁶ believe that both types probably represent the same condition. Clinically, acute porphyria is characterized chiefly by gastro-intestinal disturbances and central nervous system involvement. While there may be spotted pigmentation, the skin is little affected, and the patients rarely show light sensitivity, but do excrete large amounts of uroporphyrin Type III, especially during the acute phase. It is a familial disease, probably inherited as a dominant Mendelian characteristic. Turner states that the acute manifestations are relieved by intravenous calcium therapy.

Chronic Porphyria. This type of porphyria occurs in patients whose condition cannot be classified either as congenital or acute and is characterized by an increased excretion of porphyrins (coproporphyrin Types I and III; uroporphyrin Types I and III in various reported cases.³⁷ Patients with this type of porphyria are somewhat sensitive to light, responding with hydroa-like lesions.

Chronic Polymorphic Light Eruptions. Although various dermatological pioneers ascribed cutaneous affections of an eczematous character to light,^{200,206} it remained for Rasch in 1900¹⁵⁵ to group a number of these eczematous dermatoses under the heading of "eczema-like polymorphic light-eruption," which his pupil Haxthausen⁷⁶ subsequently clarified. Rasch included in his concept a "rash, which causes intense itching, consists partly of oval and round, slightly raised, erythematous spots of variable size, partly of irregular grouped vesicles and partly of small scab-covered papules. On the hands, which are diffusely swollen and cyanotic, there are found numerous infiltrated, or urticarial, erythematous plaques and remnants of pustules with a small central dimpled scab." He believed that one should group all light-induced eruptions of a papular, erythematous lichenoid and urticarial type under the collective term, "chronic polymorphic light dermatitis." Haxthausen classified under this concept Hutchinson's summer prurigo, eczema solare, prurigo æstivale and summer acne. Rasch believed that certain skins reacted to the same stimulus with different manifestations but Urbach and Konrad¹⁹⁵ have seen patients with alternation of lesion types in different attacks.

The literature on this subject has become extensive and much of it consists of case reports. Among the chief recent contributions are those of Rasch,¹⁵⁵ Urbach and Konrad,¹⁹⁵ Turner,^{189b} S. Epstein,⁴⁸ and Blum.^{19a}

Blum^{19a} has, we believe, collated convincing data to show that there is a sound reason for collecting these cases into one group. He states that most of the patients respond abnormally to the sunburn spectrum. A few of them, however, react abnormally to other wave-lengths. Urbach and Konrad¹⁹⁵ found their patients sensitive to wave-lengths between 4900 and 7000 Å. Templeton and Lunsford¹⁶⁶ found 1 of their 2 patients sensitive to sunlight but not to wave-lengths longer than 3340 Å. Shaumann and Lindholm's¹⁶⁸ patient was sensitive, according to Blum, to the sunburn spectrum. These authors in 1938 demonstrated absence of sensitivity to visible radiation. Turner^{189b} felt that the sun "causes the pruriginous eruption by acting on a 'primary reacting substance' whose absorption spectrum shows a sharp rise and fall between 3020 Å and 3125 Å."

The mechanism underlying the production of this type of light-sensitive dermatosis is unknown. There are some^{48,91,95} who maintain from their experience that allergy plays an important rôle, and the definite reports of passive transfer of the sensitization^{29b,51} point to this conclusion. Turner^{189b} stated definitely, on the other hand, that this is not a condition properly described as "physical allergy." Mühlman and Akobjan¹³⁵ rendered rats sensitive to the mercury arc irradiation by injecting blood serum from a patient with prurigo æstivale. Rasch thought there was an hereditary factor in some of the cases. Jausion and his co-workers^{91,95} have attempted to demonstrate a bacterial origin for polymorphic light eruptions and recommended gold therapy. Riccioni¹⁵⁷ suggested an endocrine factor in the cause. Porphyrinuria has been demonstrated in some of the patients, but no evidence has been produced to prove that the eruptions are due to a photosensitizing substance.

Photosensitivity in Pellagra. The connection between sunlight and the dermatitis of pellagra was first noted according to various reviewers^{72, 73, 125a, 177} by a number of authorities about 1771 to 1794.^{1, 38, 56, 183} In 1792 Gheradini⁶¹ produced skin lesions and other signs and symptoms of pellagra in 10 pellagrins by exposure to the sun's rays. In 1794 Strambio¹⁸³ produced skin lesions repeatedly on various parts of the body by exposure of pellagrins to the sun. Since these historic beginnings the influence of the sun's rays on the lesions of pellagra has been a subject of debate. Smith and Ruffin's¹⁷⁷ admirable summary of this relationship states:

Casal noted a seasonal variation in the incidence of pellagra, with a peak which corresponded to the spring equinox. In Italy one of the common names applied to this disease by the peasants is *mal del sole* (disease of the sun), while certain Italian physicians have described the lesions as due to "sunstroke of the skin." Many modern clinicians have stated their conviction that there is a close relationship between exposure to sunlight and the development of cutaneous lesions in a pellagrin. Various observers have produced typical cutaneous lesions in a pellagrin by exposing normal or recently healed areas of skin to direct sunlight. Gherardini demonstrated the effect of the sun by systematically uncovering various parts of the body of each patient. Bouchard, Hameau and Ormsby had their subjects wear fenestrated gloves; Wilson had them expose both arms, and we have produced typical lesions in subjects by having each expose one arm to direct sunlight. Randolph prescribed a sun bath for a Negro with pellagra. After a short period of exposure the patient complained of intense burning of the skin, and he was promptly removed to a dark room; nevertheless, severe dermatitis appeared and was followed by stomatitis, diarrhea and dementia. The patient finally recovered.

The presence of lesions on unexpected portions of the body, such as the elbows, knees, sacrum, scrotum and perineum, has led certain students of pellagra to deny the influence of sunlight in the production of the dermatitis. Tucker, Enright and Goldberger and Sebrell recognized that an existing lesion can be accentuated by exposure to sunlight, while Spies stated that the cutaneous lesions heal equally well regardless of whether the patient is kept in the dark or exposed to direct sunlight. Bigland and Spies failed to produce lesions in pellagrins by exposing them to sunlight, and Gougerot, Burnier and Meyer, Crutchfield, Bassi and Spies reported that they noted no unfavorable response to ultraviolet radiation.

From their own studies on 35 pellagrins, Smith and Ruffin found that a moderate exposure to the direct rays of sunlight resulted not only in dermatitis but in an exacerbation of the constitutional symptoms of the disease in 13 of the patients. In 2 other patients this exposure produced the constitutional symptoms, but no dermatitis. Balbi⁸ tried to determine the relationship between sunlight and pellagra by utilizing the observation of Jobling and Arnold,⁹⁷ that improvement occurred when pellagrins were kept in a dark room. He hospitalized 7 patients in the dark for 8 to 10 days and noted the cutaneous lesions daily. The diet was controlled and no special treatment was given. The patients were permitted to leave their rooms in the evening. All the patients were improved.

Efforts to produce pellagra lesions due to light in lower animals likewise have yielded inconclusive results. Mathews^{125c} who reviewed the experimental studies came to the conclusion that it is possible that the ill-effects of a corn ration and exposure to light may represent the combined action of malnutrition and heat rather than photodynamic sensitization.

The interesting finding by Jobling and Arnold⁹⁷ of an aspergillus from the digestive tracts of pellagrins, which produced a fluorescent substance on artificial media, has not been confirmed. The authors considered these results to be of etiologic importance in pellagra, since the fluorescent substance proved to be photodynamic on injection into rats. Mathews^{125a} considers such results of little value because the fluorescent substance was not administered through the digestive tract.

The association of light sensitivity with increased porphyrin excretion has stimulated much interest in the problem of porphyrin metabolism in pellagra. As early as 1932 increased porphyrinuria was noted in endemic pellagrins in Italy.¹²⁴ This observation was apparently confirmed by others, particularly by Beckh, Ellinger and Spies.¹² Recent studies have thrown considerable uncertainty on the rôle of these porphyrins in causing the dermatitis of pellagra. Furthermore, the increased excretion of porphyrins has been found particularly in alcoholic pellagra, as well as simple alcoholism; and since excretion of coproporphyrin III occurs in intoxications associated with damage to the liver, a malfunction of the liver sufficient to interfere with normal handling of the porphyrins is thought to occur in pellagra (Rosenblum and Jolliffe¹⁶²).

Another factor involved in pellagra and porphyrin metabolism is the relationship of nicotinic acid to pigment excretion. This subject has been thoroughly covered by the review of Elvehjem.⁴⁶

Beckh, Ellinger and Spies (1937) reported an increase in the amount of coproporphyrin 1 or 3 in the urine of pellagrins and a decrease following the treatment of the pellagra with yeast or liver extract. Later Spies, Gross and Sasaki (1938) found that nicotinic acid also produces a decrease of porphyrinuria in pellagrins. They also found that the porphyrinuria associated with other diseases promptly decreased following nicotinic acid therapy. Watson (1938) found that the urinary coproporphyrin in alcoholic pellagrins was not correlated with the Beckh-Ellinger-Spies test. In a later paper Watson (1939) concludes that the color reaction observed in the urine during pellagra is due to urosein. It occurs as a chromogen which changes to a pink or red pigment upon addition of hydrochloric acid to the urine. Another pigment soluble in chloroform may also be present which appears to be indirubin. Both of these pigments may be noted in the urine of patients not having clinical pellagra and therefore further work is necessary in order to relate the appearance of pigments directly to nicotinic acid deficiency. Meiklejohn and Kark (1939) have also found substances in the urine of pellagrins capable of giving the urosein reaction. They were unable to find any unusual amount of coproporphyrin in four samples of urine supplied by Dr. Spies and suggest that it would be more proper to refer to the Beckh-Ellinger-Spies test as indicating the presence of pigments capable of producing the urosein reaction.

Experiments carried out by Kühnau¹⁰⁸ in which mice were given injections of photodyn, one group of the animals being given injections of nicotinic acid amide at the same time, and all the animals exposed to the sun's rays for 15 minutes, indicated that the injurious effect of photodyn was not neutralized by nicotinic acid amide, but on the contrary the mice which received both injections died sooner than those which did not. When the nicotinic acid amide was given within 10 minutes after the photodyn, and the animals exposed to the sun $\frac{1}{2}$ hour later, some differences were noted in the behavior of the two groups. Although the animals treated with nicotinic acid amide did not survive, the course of the sun injury was milder, and death occurred later than in the untreated group. Kühnau¹⁰⁸ concluded that nicotinic

acid amide is apparently an indispensable factor in the protection of the normal skin against ray injuries, but that no unequivocal relationship can be established between this vitamin and porphyrin metabolism.

Urticaria Solaris. Urticarial wheals are rarely produced by exposure to sunlight. Many of the text-books and studies on dermatology scarcely mention urticaria due to light.^{84,192a} Pillsbury and Sternberg¹⁴⁹ in their discussion on papular urticaria stated that sunlight has been considered by several investigators as a cause of this condition, and while they were not prepared to dismiss light as a factor, they did not believe it to be the principal cause. The question of light urticaria has recently, however, become the subject of much interest. Extensive studies have been published by Blum,^{19a} Blum, Allington and West,²⁰ Blum and West,²⁴ Epstein,⁴⁸ Arnold,⁵ and Rajka.¹⁶⁴

The definition of urticaria solaris as given by Blum^{19a} identifies it with the triple response (Lewis) produced by blue and violet light. S. Epstein classifies this condition among the allergic light dermatoses. The first case reported was that of Merklen¹²⁹ (1904). Among the other authentic cases reported were those of Ward,²⁰² Ochs,¹³⁷ Duke,⁴³ Frei,⁵⁷ Beinhauer,¹⁴ Vallery-Radot^{198,199} and his co-workers, Wucherpfennig,²⁰⁸ Weiss,²⁰³ Blum and co-workers,^{20,24} Epstein,⁴⁸ Arnold,⁵ and Rajka.¹⁶⁴

In solar urticaria exposure of the skin to sunlight for brief periods is followed within a few minutes by the appearance of erythema limited precisely to the exposed area. The erythema is replaced shortly by edema, limited to the irradiated area and as the edema develops, a flare occurs in the surrounding unexposed skin. The amount of sunlight needed to produce the response is small, and the reaction is independent of the patient's health, age, and sex. Many attempts have been made to determine the portions of the spectrum which are responsible for the urticarial lesions. Ward²⁰² and Ochs¹³⁷ found that "violet light" produced urticaria in their patients. Duke⁴³ found that his patient probably was affected by the spectral regions from about 3200 to 5000 ÅU and the far-red and infra-red. Beinhauer's¹⁴ patient was sensitive to the ultraviolet portion of the spectrum. Frei thought that the short visible and long ultraviolet radiations (3200 to 6000 ÅU) were operative in his case. Vallery-Radot^{198,199} and his co-workers found the effective wave-lengths to extend throughout the visible spectrum, ultraviolet and infra-red radiations being ineffective (4000 to 5000 and 4000 to 7000 ÅU). Wucherpfennig's²⁰⁸ patients showed greatest sensitivity to the long ultraviolet, but also to other light rays which darken photographic plates. Epstein⁴⁸ found wave-lengths of 4000 to 4500 ÅU as well as ultraviolet radiation probably, to be effective. Blum and West,²⁴ in their careful study, determined that the spectral region effective in eliciting wheals was between 3900 and 5200 ÅU. Arnold⁵ found his patient's sensitivity to lie in the portion of the spectrum from 3800 to about 5000 ÅU. Rajka¹⁶⁴ determined that his patient's urticaria was produced by rays between 4000 and 5000 ÅU, and occasionally by wave-length 4359 ÅU lying in the blue spectrum and abundantly emitted by the mercury arc.

In their study of the various factors involved in the production of urticaria solaris, Blum and his co-workers^{19a,20,24} found that temperature had little effect on the threshold time, but had great effect on the latent period which precedes the appearance of erythema. They found

that the photosensitivity of different parts of the body varies widely. The abdomen and the lumbar region are more than 20 times as sensitive as the face and hands. In addition, they noted that there may be a local decrease in photosensitivity, without affecting the reaction of the rest of the body. They presumed that the sensitizing substance was a carotinoid, since the absorption spectrum of carotenoids lies almost entirely within the blue and violet band.

Duke⁴³ was the first to call attention to physical agents as the cause of urticaria, and he, as well as other authors, have collected evidence to demonstrate allergy in their cases. Others, however, have failed to produce satisfactory proof that the conditions in their cases were based on allergy.¹⁹⁴ This same difference of opinion has extended to the question of the allergic or non-allergic nature of light urticaria, as well as of other dermatoses with a light sensitization factor. (See Part I, Blum and Epstein, sulfanilamide.) Blum^{19a} has decried the "allergic," viz. idiosyncratic, nature of urticaria solaris. On the other hand, Jausion and Pagès,⁹⁴ Epstein,⁴⁸ and more recently Rajka¹⁵⁴ have been strong advocates of the "photoallergic" concept. Some of the reported cases give a personal or familial history of allergy, and passive transfer in light urticaria has been accomplished.¹⁵⁴ Bernstein¹⁸ reported passive transfer to guinea-pigs. In Rajka's¹⁵⁴ case there was whealing, accompanied in addition to the passive transfer, by hemoclastic crisis and general symptoms. Rajka succeeded in partial desensitization.

There is a distinction between urticaria solaris and the urticarial reaction occurring after local injection of photodynamic substances followed by radiation. In the latter case the whealing results in pigmentation which is a sequel to epidermal injury. No pigmentation follows spontaneous urticaria, and the wheals resulting from histamine injection.²⁰ This is considered by Epstein to favor the allergic nature of urticaria solaris.

Photodermatitis. Photosensitization by Substances Coming in Contact with the Skin; Berlock Dermatitis; Dermatitis from Vegetable and Other Substances (Fig Dermatitis; Dermatitis Bullosa Striata Praten-sis [Meadow Grass Dermatitis]).

For about 25 years dermatologists have shown an increasing interest in photodermatitis induced by the local application on the skin of certain plant substances and subsequent exposure to sunlight. The noxae were thought to be an aromatic oil or some oleoresinous portion of the plant to which the cutaneous surface was exposed. Freund described the most common of this variety of photodermatitis, Berlock dermatitis,¹⁶³ which follows the application of certain toilet waters and perfumes and subsequent exposure to sunlight. The first case of Berlock dermatitis observed in this country was reported by Gross and Robinson.⁶⁹ In 1926 Oppenheim^{139a, b, 140a, b, c} described meadow grass dermatitis (*dermatitis bullosa striata pratensis*), and eruption occurring in persons taking sunbaths who were at the same time in contact with certain meadow plants. Kitchevatz^{104a, b, c, d, e} since 1934 published a series of studies on a photocatalytic dermatitis due to contact with figs. The literature on this whole subject has become extensive. Some of the more important contributions in recent years are: (a) Berlock dermatitis, Gross and Robinson;⁶⁹ Greenbaum;^{65b} Rogin and Sheard;¹⁶¹ Goodman.^{64a, b} (b) Meadow grass dermatitis, Corson;³² Robinson.¹⁵³

(c) Fig dermatitis, Kitchevatz,^{104d,c} Behcet, Ottenstein, Lion and Des-sauer.¹³ (d) Various plants, Kuske;^{109a,b,c} O'Donovan.¹³⁸ (e) Parsnip, Hirschberger and Fuchs;⁸² Jensen and Hansen.⁹⁶ (f) Lime oil, Sams.¹⁶⁶

The excellent papers by Oppenheim,^{139b} S. Epstein,⁴⁸ Sams,¹⁶⁶ and the chapter in Blum's book^{19a} are complete reviews of this subject and deserve careful study.

The various photodermatitides are considered in one place because, while their clinical manifestations are somewhat varied, fundamentally their modes of production are relatively similar. The photodynamic effects of externally applied hydrocarbons will be discussed in connection with cutaneous cancer. In Part I of this review,^{180a} it was stated that Guillaume⁷⁰ showed that a photosensitizer must reach the Malpighian layer of the epidermis in order to produce observable effects, and no photodynamic responses occur unless the layer is exposed, by abrasion or otherwise, to the action of the substance. Accordingly, photodermatoses are not regularly produced by external contact because most substances do not penetrate below the corneous layer. There are, however, photosensitizing substances which do penetrate below the corneum and effect photosensitization.

Berlock Dermatitis. This peculiar pigmentation resulting from the successive action of application of toilet water and exposure of the skin to sunlight or to artificial ultraviolet irradiation, is usually found on the neck and chest, and appears as dark red spots, changing to brown, slightly mottled with red. The shape of such discoloration simulates a small drop of flowing fluid. Berlock dermatitis generally appears during the summer.

The exact pathogenesis of this dermatosis is unknown. It is believed that one is dealing with a personal susceptibility or with various factors such as climate, perspiration, brand of perfume or some contaminant of the perfume, and short intervals between the application of the perfume and exposure to sunlight. Most of the evidence favors a personal predisposing factor (Gross and Robinson,⁶⁹ Greenbaum,^{68b} Wise and Sulzberger,²⁰⁷ Rogin and Sheard¹⁶¹). The photosensitizing substance is likewise undetermined, but the process may be reproduced in susceptible individuals by the local use of bergamot or citron oil followed by irradiation (Freund,⁵⁸ Del Vivo³⁶).

Some investigators believe impurities, copper (Goodman^{64b}) or chlorophyll,¹⁶¹ in oil of bergamot may be the inciting factor. On the other hand, the application of bergamot oil without trauma, *i. e.*, friction, does not produce any reaction without exposure to light. According to Del Vivo³⁶ bergamot oil sensitizes the skin to blue and violet light.

Photodermatitis of Vegetable Origin. Since Oppenheim first described dermatitis following sunbathing in meadows and fields, studies have appeared either describing new plants as sources of such trouble, and presenting data to indicate the possible mechanism or wave-lengths involved.^{25,104,166} Cases have been reported from many lands: Germany, France, Russia, Denmark, Italy, Spain, Switzerland, Austria, all other European countries and the United States.^{32,139b,155}

Meadow Grass Dermatitis.—This process has recently assumed a military importance as was suggested by Hirschberger and Fuchs⁸² and Englehardt.⁴⁷ The former noted lesions in soldiers who had used green plants, including parsnip, in camouflage. Englehardt⁴⁷ found that 45 of

120 soldiers, drilling on a meadow near a beach, developed a vesicular dermatitis a few hours later. Blum advisably points out that the lesions of meadow grass dermatitis may cause confusion because they resemble those produced by mustard gas. The sharp circumscription of the lesions and the resulting persistent pigmentation of meadow plant dermatitis tend to differentiate it from the plant dermatitis of the primrose type, and point to a photodynamic origin.^{35,47} (See Gorodinsky,⁶⁵ whose patient had an experimentally reproducible linear bullous dermatitis from *Dictamnus fraxinella caucasicus* without the use of sunlight.)

Patients with meadow grass dermatitis give a history that they developed pruritic bullæ in more or less striated arrangement, appearing the day after the sunbath. The process clears readily, but leaves pigmentation which may persist for months. It is not produced at seashores or other places where sunbaths are taken, if there is no opportunity for contact with plants. Kuske^{109a,b,c} describes the chief clinical characteristics of exogenous percutaneous photosensitivity from plants as being (1) latent period, on an average of 7 to 12 hours; (2) the acme which depends on the intensity of irradiation and manifests itself as edematous swelling ranging to bulla formation; and (3) residuum, of long-continued pigmentation.

The exact cause of meadow grass dermatitis is unknown. Oppenheim originally thought it was due to an animal parasite (Milben) but later¹⁴⁰ he leaned toward a plant or plant product as the source of the dermatosis.^{26,54,60,121,145,176} Philadelphia intimated that sunlight might play a rôle in the cause of the eruption but Kitchevatz^{104c} made the first extensive experimental studies. He showed that the red rays of the spectrum acting through an intermediate catalytic substance, chlorophyll, rendered the skin more sensitive. The photosensitization occurs only where chlorophyll is placed in intimate contact with the cells of the skin. Acid increases the action and the sensitivity cannot be passively transferred. Kitchevatz's explanation for this process is not accepted by many.^{13,82,92,93,96,139a,140} Hirschberger and Fuchs⁸² in studies with parsnip plants (*Pastinaca sativa*) thought that the active agent was flavone. Oppenheim^{139b} believed that sensitivity to etherial oils in plants was the basis for the dermatosis. Cummer and Dexter³⁵ asserted that the active substance was an aromatic oil but could not prove this experimentally with extracts of the gas plant applied to the skin. Kuske^{109a,b,c} in a series of detailed studies employing juices from 5 plants concluded that phytogenous photosensitization was due to the presence of similar sensitizers, furocumarines. He showed that the furocumarines sensitize human skin for ultraviolet long waves, especially in the spectral field around 3340 and 3660 ÅU. Jensen and Hansen⁹⁶ studied the active spectral range for dermatoses produced by the parsnip plant, and found the wave-lengths which produce the lesions to lie in the ultraviolet longer than 3200 to 3600 ÅU. Blum^{19a} calls attention to the fact this spectral region does not correspond to the absorption spectrum of chlorophyll nor with the sunburn spectrum. Sams¹⁶⁶ presented a study of 11 patients suffering from photodermatitis due to oil from the Persian lime (*Citrus aurantifolia* var. *Sicingle*). He was able to reproduce the photodynamic reaction experimentally and showed that the concentration of the photodynamic agent, the length of time of exposure,

the subject, the location of the application, and previous radiation determined the intensity of the subsequent dermatitis. The longer wave-lengths of ultraviolet radiation (3100 to 3700 ÅU) are involved in the production of the dermatitis and subsequent pigmentation. The chemical nature of the photocatalytic agent is still undetermined.

Sunlight and Cancer of the Skin. It has been repeatedly contended since 1894 (Unna¹⁹¹) that prolonged exposure to the sun may stimulate the production of malignant tumors. Blum^{19c} has collected and critically analyzed this entire subject. His study and the résumé in his book^{19a} are the chief sources of this discussion. Other recent studies of the relationship of cancer to irradiation are those of Körbler,¹⁰⁷ Büngeler,²⁸ Roffo and Luchetta,¹⁶⁰ Poth,¹⁵⁰ Rusch and Baumann,¹⁶⁴ Rusch, Kline and Baumann,¹⁶⁵ Doniach,³⁹ Teutschlaender,¹⁸⁷ Whitmore,²⁰⁵ Grady, Blum and Kirby-Smith,⁶⁷ Blum, Kirby-Smith and Grady,²² Hueper,⁸⁶ Apperly.⁴

Since the description of "Seaman's skin" by Unna¹⁹¹ as a precancerous condition attributed to continued exposure to light, some authorities^{15, 40, 41a, b, 90, 114, 132, 146, 160, 175} have emphasized the rôle of sunlight among the factors causative of cancer while others have opposed this view.

The evidence for the rôle of sunlight in the production of skin cancer has been entirely clinical, *i. e.*, it has consisted of attempts to correlate clinical findings with intensity of exposure and susceptibility to sunlight. Roffo,^{159a, b-c} especially convinced of the importance of the influence of the sun, based his opinion on three principal arguments: (1) malignancy of human skin appears most frequently on those parts of the body most exposed to light; (2) malignancy of the skin may be produced in laboratory animals by prolonged exposure to light; and (3) there is an apparent direct relationship between cholesterol content, exposure to light, and the incidence of malignancy. In addition, Blum^{19c} has deduced from the literature that those in favor of sunlight as a carcinogenic agent state that cancer of the skin is more prevalent in outdoor workers and that the incidence is higher in regions of the earth which receive greater insolation and it occurs more frequently in blondes than brunettes. Blum believes that the clinical facts cited in support of these claims are still open to question, but that within recent years support has come to the theory of direct causation of cancer by sunlight from experiments on laboratory animals. These studies not only demonstrate that cancer can be caused by sunlight, but offer opportunity to study the various factors involved.

Artificial production of cancer in animals was first accomplished by Findlay⁴⁹ in mice. His work was followed by similar studies independently conceived and prosecuted.^{19c, 79, 152, 159a, b-c} More recently similar successful experiments were made by Huldshinsky,⁸⁷ Beard, Boggess and von Haam,¹⁰ Rusch and Baumann,¹⁶⁴ and Rusch, Kline and Baumann.¹⁶⁵ Roffo^{159d, e} showed that natural sunlight, as well as mercury arc radiation, may cause tumors in rats. The tumor lesions were chiefly confined to bald or sparsely hairy parts of the animals (eyes, ears, paws or parts shaved for experimental purposes). The tumors were either epitheliomas or sarcomas, and were transferable to normal rats.^{159f} The active wave-lengths were found to be in the region of the sunburn spectrum. Rusch, Kline and Baumann¹⁶⁵ found the carcinogenic wave-lengths to be between 2900 and 3341 ÅU. Very little

radiant energy was needed to initiate the changes which culminate in tumor formation. The length of the precancerous period varied inversely with the daily dose of radiant energy. The minimum time for the development of tumors appeared to be about $2\frac{1}{2}$ months. It was not necessary to irradiate the animals throughout the precancerous period; once initiated, carcinogenesis proceeded without further exposure to radiant energy and in isolated cases several months elapsed between the end of radiation and the appearance of tumors. Grady, Blum and Kirby-Smith⁶⁷ found by a specially controlled method of exposure of mice to mercury arc radiation that a 100% incidence of tumors may be induced on the ears of "male strain A" mice by such radiation. At higher dosages of radiation, the time of appearance of the tumor is little affected by the dosage, but at lower dosages this time increases markedly with decreasing dosage. They also showed that the production of tumors depends upon the quantity of radiant energy applied rather than upon the intensity of the radiation. The tumors thus produced were chiefly fibrosarcoma, less frequently combinations of fibrosarcoma and squamous cell carcinoma and rarely squamous cell carcinoma alone.⁶⁷

The type and quantity of radiation (sunburn radiation) are not the only factors involved. So far only rats and mice have been shown to be definitely susceptible to tumor production, although suggestive results have been obtained in other animals. The color of the animal is important, since Rusch and Baumann¹⁶⁴ found that considerably more radiation was required for tumor production in C 37 brown mice than for strain A and strain C albino mice. They also found that black mice developed a smaller percentage of tumors than albinos and that the time required was greater. The color of the hair may have served as a filter in the case of the colored mice. Rusch, Baumann and Kline¹⁶⁵ found that the rate of tumor production with ultraviolet light could be altered by the local application of certain substances to the tissues developing tumors. Mineral oil accelerated tumor development most rapidly. Cholesterol in oil caused acceleration, other substances and oils were less stimulative and linseed oil retarded tumor formation. Baumann and Rusch¹⁶⁴ found that the rate of tumor development varied with different diets. Lesions were produced more rapidly on a high fat diet, while brain extract or liver retarded tumor production. Addition of 2% cholesterol to the stock diet did not affect the rate of tumor production, although a marked increase in liver fat and cholesterol resulted. These results suggested that the rôle of cholesterol in tumor production was a limited one in contrast with those of Roffo who claimed that (a) the cholesterol content of tumors and precancerous lesions is higher than that of normal tissue; (b) tumors may be induced in man and animals with light alone as a carcinogenic agent; (c) the cholesterol content of the skin exposed to light is higher than that of skin protected from light. Bergmann¹⁶ denied the importance of the belief that cholesterol is changed into a carcinogenic agent in the skin by irradiation. In summary, Blum^{19c} asserts that "while the idea that sterols in the skin may be changed to carcinogens by the action of ultraviolet light is an attractive one, it must be admitted there is little evidence in its favor at present." The same applies to Körbler's¹⁰⁷ suggestion that porphyrins might be photosensitizing agents for cutaneous tumor production.

In connection with human cancer and sunlight, there are a number of factors of importance. Among them are: geographic distribution of sunlight; distribution of cutaneous cancer and its relationship to sunlight; the character of the skin; season, sex, menstruation (irregular increase in sensitivity), pregnancy (sensitivity increases after the third month), and advancing age (decreases) (Ellinger⁴⁵).

Lawrence¹¹⁴ discussed the low humidity and abundant sunshine as a causal factor for cancer of the skin in Australia. The moisture in the atmosphere impedes the passage of ultraviolet rays. He found that rodent ulcer is over 20 times as frequent in dermatologic practice in Australia as in England. Molesworth¹³² and Duhig⁴² confirm Lawrence's opinion. Duhig⁴² found that 25 % of hospital admissions for cancer at Brisbane are cases of skin cancer. The same state prevails in our own arid Southwest.¹⁷⁸ The incidence of skin cancer is 3 to 4 times as great in Atlanta, Georgia as in the northern city of Chicago, Illinois.¹³⁴ Peller, Stephenson and Souder^{141,142,143} have recently reviewed the incidence of cancer of the lip and skin in the United States Army and Navy and found that such cancer occurs more frequently among soldiers and sailors born and who presumably resided in their early years in southern states than among those born in northern states.

Blum critically reviews the claims that skin cancer is more prevalent at regions of the earth that receive greater insolation and points out that "seldom are these supported by statistics of cancer incidence, and there do not exist sufficient data of cancer on the intensity of the tumor-producing wave-lengths incident at different regions of the earth to permit a real correlation. The distribution of total sunlight can be estimated with some accuracy but this is much more difficult for the wave-lengths that produce tumors."

Apperly^{4a} has made an interesting study of the relationship between solar radiation and cancer mortality in North America, in which he points out that several observers have noted that the incidence of cancer of the various organs among peoples of European origin varies considerably with geographic location, although the total cancer death rate shows comparatively minor variations. Furthermore, Peller in a small series of cases showed that environments and occupations in which skin cancer is more prevalent, other cancers are relatively less prevalent. Others have noted the converse—that cancer of the skin does not protect against visceral cancer. The total cancer mortalities of various American states and Canadian provinces are shown to fall with increasing solar radiation and with the number of people exposed thereto, and are independent of the production of skin cancer. Apperly⁴ from his statistics concludes that we may be able to reduce our cancer deaths by inducing a complete or partial immunity by exposure of suitable skin areas to sunlight or the proper artificial light rays of intensity and duration insufficient to produce actual skin cancer. In another study, Apperly^{4b} found that when mortality rates of pernicious anemia and skin cancer (corrected for other causes than exposure to sunlight) are correlated, it appears that the incidence of pernicious anemia is closely related inversely to effective solar radiation.

Distribution of Cutaneous Cancer and Its Relation to Sunlight. Most skin cancers appear on the human face, one of the most exposed areas of the body. Furthermore, certain areas of the face are more frequently the sites of cancer than others (regions about nose and

eyes^{19c}). Aside from the possible action of sunlight,^{41,110} other factors may be involved in the localization of cutaneous cancer to the face: (1) basal cell cancer occurs along embryonic lines of closure of facial skin;^{62,119,126} (2) cancers that develop around the nose and eyes developed from embryonic rests; (3) shading of certain areas by anatomic (chin shades neck) or artificial (caps and hats) coverings; (4) certain factors preventing absorption of effective wave-lengths. Thickness of the epidermis, particularly the corneum, on different parts of the face might be of importance in determining the location in skin cancer if sunlight is an important etiologic factor; (5) certain dermatoses (lupus erythematosus) have similar distribution; (6) exposed parts are affected by minor traumata.

The Character of the Skin and Cancer. The relationship of the skin color to light sensitivity has been discussed in the first part of this review. With specific reference to skin cancer, Taussig and Williams¹⁸⁵ stated that it is more common in blondes than in brunettes. Hyde⁹⁰ commented on the result of cutaneous cancer in Negroes. This has been reaffirmed by many others.^{77,111,132,144,159,167}

Occupation and Cutaneous Cancer. It is difficult to ascertain whether occupations subjecting persons to greater exposure to sunlight are predisposing to cancer. There are statements pro and con; by equally competent observers.^{86,119,142,209} The occupation may present other factors than sunlight to account for cancer-occurring in the face. For example, the handling of tar preparations^{28,39,187,209} which produces a cancer limited largely to the exposed parts (but compare scrotum).

The pathogenesis of the production of cutaneous cancer by sunlight is not definitely determined. There are many hypotheses to explain the process and certain important data have been collected from animal study. However, more exact information, clinical and experimental, is needed for the solution of this problem.

Xeroderma Pigmentosum. Xeroderma pigmentosum is a rare cutaneous affection which appears early in life and terminates in malignancy, so that persons affected with it usually die by their 15th year. These individuals may show successively or simultaneously erythema, pigmentation, atrophy or tumor formation. Photophobia may be a prominent symptom. Xeroderma pigmentosum is an inherited abnormality, and Cockayne³¹ has shown that it is a recessive character due to a single gene and it is not sex-linked. It occurs frequently in the product of consanguineous parentage.

Kaposi⁹⁹ who first described xeroderma pigmentosum failed to note its frequent onset after solar exposure.¹³³ The first to suggest this relationship was Unna¹⁹¹ (1894) but subsequent investigators had various experiences from attempts to demonstrate abnormal reactions to light. The results of these studies are summarized in the publications of Lynch,¹¹⁸ Mathews,^{125a} King and Hamilton,¹⁰² and Blum.¹⁹² Blum concludes that these studies leave open the possibility that sunburn radiation precipitates the lesions of xeroderma pigmentosum. It seems most probable "that the abnormal response is the result of some abnormality of the skin which is exacerbated by the action of the sunburn radiation, but that the condition might develop independently of this radiation although its appearance may be accelerated by it" (Blum¹⁹²). Lynch¹¹⁸ found that the sensitivity was to wave-lengths

2800 to 3100 ÅU. Zoon²¹⁰ found an increased sensitivity to the long wave-length sunburn spectrum (around 3000 ÅU).

Pigmentation Due to Photosensitization. The normal pigmentary response of the skin to sunlight is not considered here. There are, however, a number of circumstances of widely different character leading to hyperpigmentation, in which light plays a prominent rôle. Other pigmentary dermatoses provoked by light and externally applied sensitizers (Berlock dermatitis, meadow grass dermatitis) have been discussed.

In 1913 Lewin¹¹⁶ noted that workers employed in the manufacture of electrical cables involving coal-tar and petroleum products were sensitive to light. Similar observations were made by Kistiakowski,¹⁰³ Mierzecki¹³⁰ (petroleum products), and Foerster and Schwartz.⁵³ Fleischhauer⁵³ showed that only coal-tar products are photosensitizing while wood tars are not. Foerster and Schwartz⁵³ examined more than 500 men in 4 factories; more than half of them had either melanosis or cutaneous lesions, chiefly dermatitis. The condition was confined to handlers of pitch or of pitch products, but those most intimately in contact with pitch were affected the least, while those who had the most severe dermatitis and the most intense pigmentation were outdoor workers. Indoor work, necessitating direct contact with pitch and pitch vapor and exposure to high temperatures, did not appear to be definitely associated with development of dermatitis. But when an indoor worker was placed at yard work, an inflammation of the face invariably followed. This disappeared, although the pigmentation persisted, when he returned to indoor work.

The dermatitis was characterized by diffuse erythema and desquamation at times associated with severe edema; it involved chiefly the face and neck particularly the nasolabial areas and chin, and was frequently accompanied by conjunctivitis and occasionally with labial herpes and cheilitis. The pigmentation was diffuse and intense, considerably darker than ordinary suntan, and it was confined to those surfaces exposed to sunlight. Pitch comedones and folliculitis on the face, neck, hands and forearms were commonly observed, and keratoses and papillomas were found occasionally. Only 2 epitheliomas were seen, and these apparently were not due to pitch or tar. While some men were affected more severely than others, apparently none sufficiently exposed were immune. Tolerance with persistent pigmentation was developed in some cases, but most of the men had to be rotated among various jobs, and some were so hypersensitive that they could not be employed in the daytime but worked satisfactorily on night shifts. Pigmentation was not permanent, but it persisted at least for several months after removal of the worker from exposure.

Similar dermatoses (melanosis of Riehl) were frequent during the last war, in Germany, according to Habermann,⁷² and were attributed to the use of impure products and adulterants because of the blockade of the Central Powers by the Allies, but since there were many cases in other countries not under blockade, Thibierge¹⁸⁸ suggested that blockade was not the chief factor. Others intimated that it might have come from contact with tar or oil. Recent studies from South America^{145,151} suggest that this process in Argentina is the result of application of cosmetics containing photosensitizing substances, the skin reaction

being provoked by sunlight. Dietary and endocrinologic factors, however, may still play a part in the production of this pigmentary state.

In 1930 Fleischhauer⁵² found that Lianthal, a coal-tar product, sensitized the skin to light (sunlight even through window glass or light from a quartz lamp) although, if it were applied in the usual manner and allowed to dry, it acted as a light protective. On the other hand, wiping the excess off after about 15 minutes, the skin was found to be light-sensitive. This photosensitization lasted for as long as 72 hours after the application. This observation (photochemical change in crude coal tar (?))⁸⁰ is the basis for the Goeckerman treatment for psoriasis in which the patient is irradiated after having been treated with a tar preparation.⁶³

The action spectrum for lesions produced by light after application of tar was found to be between 3300 and 5000 ÅU by Fleischhauer⁵² while Foerster and Schwartz⁵³ found the range in their cases to be between 3900 and 5000 ÅU.

Other cutaneous pigmentations produced through the action of light are those caused by heavy metals: silver (argyria);⁸¹ arsenic (arsphenamine dermatitis); gold;^{30,169} mercurochrome;¹⁵³ and a transient discoloration of the nails due to mercury bichloride.^{29a,98,184} This latter condition is not a true pigmentation since Callaway demonstrated that the solution of mercury bichloride coming in contact with the sulphur in the skin and nails and activated by light causes the formation of a black mercuric sulfide which is responsible for the discoloration.

Lupus Erythematosus. There has been a widespread impression recently that lupus erythematosus is increasing,^{11a,b,106,117,180,204} but Gahan's figures^{59a,b} from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital during the years 1936-1940, do not seem to substantiate such an increase, at least for the period studied. At any rate, an increasing number of investigators have been reporting the onset of some of their cases of lupus erythematosus as appearing subsequent to solar irradiation.^{6,11a,b,25,34,50,66,180} Although Hausmann and Haxthausen⁷⁵ found that in Copenhagen there is a great increase in the appearance of lesions in the spring and summer, Gahan^{59a,b} found no particular type of seasonal variation in the incidence of the disease in New York. In a study designed to determine the factor of actinic trauma in the causation or pathogenesis of lupus erythematosus, Gahan^{59a,b} found no appreciable difference between the relative frequency of the disease in the United States (0.4%) and in any other part of the world inhabited by the white race; whatever differences there may be are not based on climatic conditions. Cumer³⁴ found that, according to statistics, lupus erythematosus occurs about half as frequently in the Negro as in the white race. The deep pigmentation is a protection against the sun's rays.¹⁵⁶ In 1938 Ludy and Corson¹¹⁷ found hematoporphyrin in the urine of many of their patients with lupus erythematosus of the acute and subacute types. In these individuals the hematoporphyrin disappeared with their improvement in other respects. Ludy and Corson¹¹⁷ thought that this substance could readily account for the dermal changes and might serve as a danger signal against the use of certain treatments for lupus erythematosus. They also noted the presence of lead in the skins of

their patients, and thought that it might play a rôle in the pathogenesis of lupus erythematosus.

Other Dermatoses With Light Sensitization Factors. An inspection of the detailed classification of the light-sensitization dermatoses would indicate that there are many cutaneous diseases in which light might play a rôle. Recent studies have been concerned with granuloma annulare;^{27,105} varicella;¹²⁰ purpura solaris;¹⁷ epidermolysis bullosa;¹⁰⁰ psoriasis;^{122,173} severe actinic dermatoses (resulting from increased stercoporphyria, abnormal intestinal flora and hepatopathy);^{192b} pyogenic relapse and sensitiveness to light in certain dermatoses (discussed in Part I);¹⁸¹ lipid proteinosis;¹⁹⁷ and lymphogranuloma venereum.¹⁷⁹ Sonck points out in his monograph on this subject that a definite distinction is made between the photosensitivity produced by the sulfonamides used in treatment of lymphogranuloma venereum, and that due to the disease itself. This study is recommended to those especially interested.

Treatment of Light-sensitive Dermatoses. This aspect of the discussion of light-sensitive dermatoses naturally divides itself into general and local treatment. Since the causative mechanism and factors involved in many of the diseases which light tends to induce are not always known, one cannot always get at and remove the cause. Attention to certain organic abnormalities may cure or temporarily stop light sensitivity. Attention to gastro-intestinal (hydrochloric acid), hepatic, infective disorders (vaccines, removal of foci of infections), vitamins (nicotinic acid), and endocrine treatment plus the use of specific (antisyphilitic treatment);¹⁹³ gold chloride¹¹⁶ or non-specific treatment (histaminase, calcium, iron)⁴⁴ have proved of benefit in certain cases. Hurst⁸⁸ apparently cured his patient by progressive light desensitization. He exposed the back daily to ultraviolet rays, beginning with a 1-inch area for 1 minute, and gradually increasing the size of the area and the length of the exposure. Treatment of patients with dermatoses due to light by intramuscular injection of hydrolysates of a number of glands of internal secretion (testes, liver, thyroid, anterior pituitary and thymus) proved successful in 28 patients at the hands of Selisky.¹⁷² Lancaster¹¹³ reviewed the entire subject of estrogenic hormone therapy in sunlight eruptions of the female and found various combinations of thyroid, corpus luteum and estrogenic substance helpful in 6 cases. This estrogenic therapy was tried in only 2 males in 1 of whom it produced marked improvement and in the other, whose sensitivity to sunlight developed after a severe attack of measles, an injection of 200 international units of theelin, in water, gave temporary relief for about 2 weeks but the patient subsequently regained his normal tolerance to sunlight.

Local therapy in light-sensitive dermatoses consists of finding one or a combination of substances which will filter out the offending light rays. The ideal preparation for this purpose is one which is non-irritating, easily removable, non-staining and when applied thinly, protects the skin against the undesirable action of ultraviolet irradiation, yet does not prevent tanning. Numerous recent studies of real scientific merit have appeared from time to time, listing and stating the value of many substances including proprietary preparations.^{7,78,101,127,174,182,195}

Among the various preventives proposed are: naphtholsulfonic acid,

esculin or its homologues, lithopone, titanium compounds, menthyl salicylate, certain fluorescent compounds, amino or substituted amino, benzoic acid in mineral or peanut oil, quinine bisulphate, oak bark extract, vitamin C and cumarin in bergamot oil,¹⁰¹ bergamot oil;¹⁹⁶ denied by Miescher;¹³¹ salol (phenyl salicylate), resorcin.

In addition to the so-called protecting substance, its concentration or combination with other protections, there are factors which influence the effectiveness of a given formula. Sweat may in itself screen some of the active radiation. Crew and Whittle,³³ for example, showed that sweat definitely screened the skin against erythema-producing radiation so that a film 1 mm. in thickness transmits only about 27% of solar radiation effective in producing sunburn.

The base likewise plays an important rôle in the action of ointments intended for protection against sunlight. Bachem and Fantus⁷ found wool-fat, yellow petrolatum and diachylon ointments to have the highest sunscreen value of the ointment bases tested and yellow petrolatum was superior to white petrolatum. In a later study Strakosch¹⁸² found that petrolatum and lanolin afforded no protection against irradiation from an air-cooled mercury vapor quartz burner. Emulsions such as aquaphor (containing 6% of a group of esters of cholesterol in an aliphatic hydrocarbon base) or Abbott's Ninol base (containing fatty acid esters of monoethanolamine, mixed with petrolatum) were applied with evidence of a slight protective action. Quinine or tannic acid did not increase the effectiveness of petrolatum or lanolin and the same drugs had only slight protective action when added to equal parts of petrolatum and lanolin. When quinine or tannic acid were added to aquaphor or Ninol base (Abbott), a considerable degree of protection was afforded.

Bachem and Fantus⁷ as a result of their laboratory and clinical studies have produced 5 finished "cuticolor" preparations which are eligible for protection against light and their value seems to be similar. Choice of a given formula depends upon the effect desired. The authors claim their combinations are superior to products commercially available. The basis of the "cuticolor" preparations (lotion, paste, tragacanth paste, ointment and creme salve) is the "cuticolor" titanium dioxide the formula for which is:

Red ferric oxide	6.0 gm.
Yellow ferric oxide	8.0 gm.
Titanium dioxide	86.0 gm.
Mix by trituration.	

In addition to being efficient, Bachem and Fantus' preparations are cosmetically attractive.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, *some authorities* to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the more exact meaning.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

NOVEMBER, 1942

ORIGINAL ARTICLES

A SYNDROME CHARACTERIZED BY PRIMARY OVARIAN
INSUFFICIENCY AND DECREASED STATURE

REPORT OF 11 CASES WITH A DIGRESSION ON HORMONAL
CONTROL OF AXILLARY AND PUBIC HAIR^{*†}

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WHEN one encounters lack of sexual development together with decrease in stature, a generalized deficiency of all elements of the anterior pituitary (panhypopituitarism) naturally comes to mind as the probable primary disturbance. It is the purpose of this paper to call attention to another syndrome which has these two features but in which the sexual infantilism at least is due to primary ovarian-lack rather than to primary pituitary disease. As will appear below, this syndrome has not gone entirely without notice in the literature.

The features which characterize this syndrome are the following:

1. The patients are short in stature but not actually dwarfs as is usually the case in panhypopituitarism.

* Read before the Boylston Medical Society of the Harvard Medical School as the Presidential Address on January 29, 1942.

† This work was aided by grants from the National Research Council (Committee for Research in Problems of Sex), The Josiah Macy, Jr. Foundation of New York and the Proctor Fund. Acknowledgment is made to the Schering Corporation of Bloomfield, N. J., for the generous supplies of estradiol preparations used in this investigation.

2. They have infantile mammæ, uteri, and vaginæ; in this respect they resemble the pituitary dwarfs.

3. In spite of complete absence of breast and uterine development, they usually have a small amount of axillary and pubic hair in contrast to the pituitary dwarfs who do not have any hair in these regions.

4. They are rather strong and well nourished, in contrast to the pituitary dwarfs who tire easily and who have difficulty in putting on weight.

5. The bone age is usually a few years retarded but in most cases the epiphyses eventually unite; in the pituitary dwarf, on the other hand, the bone age is much more retarded and the epiphyses often never unite. As in other conditions with retarded bone age—hypothyroidism and panhypopituitarism—"epiphysitis" is common.

6. There is constantly present in the urine an increase above normal of follicle-stimulating-hormone (FSH); in pituitary dwarfs, of course, this hormone is absent.

7. The "17-ketosteroid excretion" in the urine¹⁵ (circa 2 to 5 mg. per 24 hours), though lower than that in normal females (circa 6 to 18 mg. per 24 hours), is considerably higher than that in pituitary dwarfs (circa 0 to 1.5 mg. per 24 hours).

8. Estrin therapy leads to the development of normal amounts of axillary and pubic hair; estrin therapy in pituitary dwarfism has no such effect.

9. The insulin tolerance test (ITT) shows normal hypoglycemia responsiveness as opposed to hypoglycemia unresponsiveness in pituitary dwarfism.¹⁴

10. Congenital anomalies in addition to the congenital absence or malformation of the ovaries are common; coarctation of the aorta and webbing of the neck are especially frequent.

11. Diffuse osteoporosis reminiscent of that seen in postmenopausal osteoporosis is common; precocious senility occurs as in panhypopituitarism.

Case Histories. CASE 1. D. W. S., No. 91914, entered this hospital in 1933 at the age of 21. She had developed axillary and pubic hair at the age of 19 but her breasts had never developed and she had never had a real menstrual period, although on several occasions she had had a slight bloody discharge from the vagina. She had been born 1 month prematurely and retarded growth had first been noted at 10; she had "stopped growing" at the age of 15.

On physical examination she was 4 feet 8½ inches; her span was 2.4 cm. greater than her height. Nutrition was excellent (see Fig. 1). There was no breast development and only a small amount of pubic hair and almost no axillary hair. The breast development and abundant pubic hair shown in Figure 1 were the result of 6 months of estrin therapy at the age of 28. Her genitalia were infantile and no uterine tissue could be felt by rectum. Blood pressure was 138/95.

When first Roentgen rayed at the age of 21, her bone age was more than 2 and less than 6 years retarded; at the age of 28 all epiphyses were closed.

The basal metabolic rate determinations were +14 and +3 respectively. An FSH test for 40 mouse units per 100 cc. of urine was positive; two 17-ketosteroid urinary assays were 4.7 and 3.9 mg. per 24 hours respectively.

While in the hospital under observation, the patient had undulant fever and the agglutination test for *Brucella melitensis* was positive. This suggested the possibility that the cause for the ovarian deficiency was a chronic infection of the ovaries with one of the brucella group of organisms. However, the patient made a spontaneous recovery from the fever and the diagnosis was never confirmed.

CASE 2. R. F., No. 133054, was first seen in 1938 at the age of 15. She was then 4 feet 6 inches tall and thought she had grown $1\frac{1}{2}$ inches during the preceding year. She had never had a menstrual period. Her parents and 2 brothers were of normal height. The patient had been born at full-term weighing 6 pounds but had always been undersized in spite of the fact that her general health had always been excellent.

She was sturdy in appearance (see Fig. 1), weighed 81 pounds; but was sexually undeveloped; there was no breast tissue and very little axillary and pubic hair; the external genitalia were infantile. Her span was 7.7 cm. greater than her height. Blood pressure was 104/70.

Roentgen ray films of her bones taken 2 years later at the age of 17 showed that her bone age was more than 4 and less than 6 years retarded. An FSH test for 10 mouse units per 100 cc. of urine was positive; two 17-ketosteroid assays were 3.9 and 3.6 mg. per 24 hours respectively.

CASE 3. C. M., No. 51984, was first seen in 1939 at the age of 22. She had never had a menstrual period and had had hot flashes since the age of 14. Rate of growth had decreased at the age of 8. Other members of her family were short but she was very much the shortest. She had been born 2 months prematurely and had had mumps at the age of 4.

On physical examination she was 4 feet 6 inches with a span 1.5 cm. greater than her height; she was fairly well nourished and weighed 88½ pounds. Her breasts were not developed and there was no axillary or pubic hair; the genitalia were infantile. Blood pressure was 120/70.

Her bone age was more than 7 and less than 8 years retarded; Roentgen rays taken 2 years later showed retardation of more than 5 and less than 9 years. In addition the Roentgen rays showed "epiphysitis" of several vertebræ (cf. Cases 4, 9, 10 and 11). The serum calcium was 10 mg. per 100 cc.; serum phosphorus, 3.9 mg. per 100 cc.; and the serum phosphatase, 6.4 Bodansky units. The insulin tolerance test showed normal findings. The basal metabolic rate was -6%. Two 17-ketosteroid assays were 4.7 and 4.7 mg. per 24 hours respectively. The FSH tests for 10 and 20 mouse units per 100 cc. were positive.

Peritoneoscopic examination showed an infantile uterus in normal position; the right tube was visualized as far as the fimbriated end; there was no evidence of any right ovary; no ovarian tissue could be seen on the left side either.

CASE 4. U. H. (see Fig. 1), No. 28130, was first seen in the Out-Patient Department in 1920 at the age of 19, at which time she complained of lack of sexual development and of retardation of growth. However, very little data were obtained at that time and it was not until 1930 at the age of 29 that any comprehensive studies were made; these led to the faulty diagnosis of panhypopituitarism. She stated that she had always been small and had never been strong.

In 1930 she was 4 feet 6 inches and weighed 74 pounds; her span was 7 cm. greater than the height. There was no breast development and the external genitalia were infantile. She had a small amount of axillary and pubic hair. She was definitely undernourished and her facies suggested premature old age as so often is seen in panhypopituitarism.

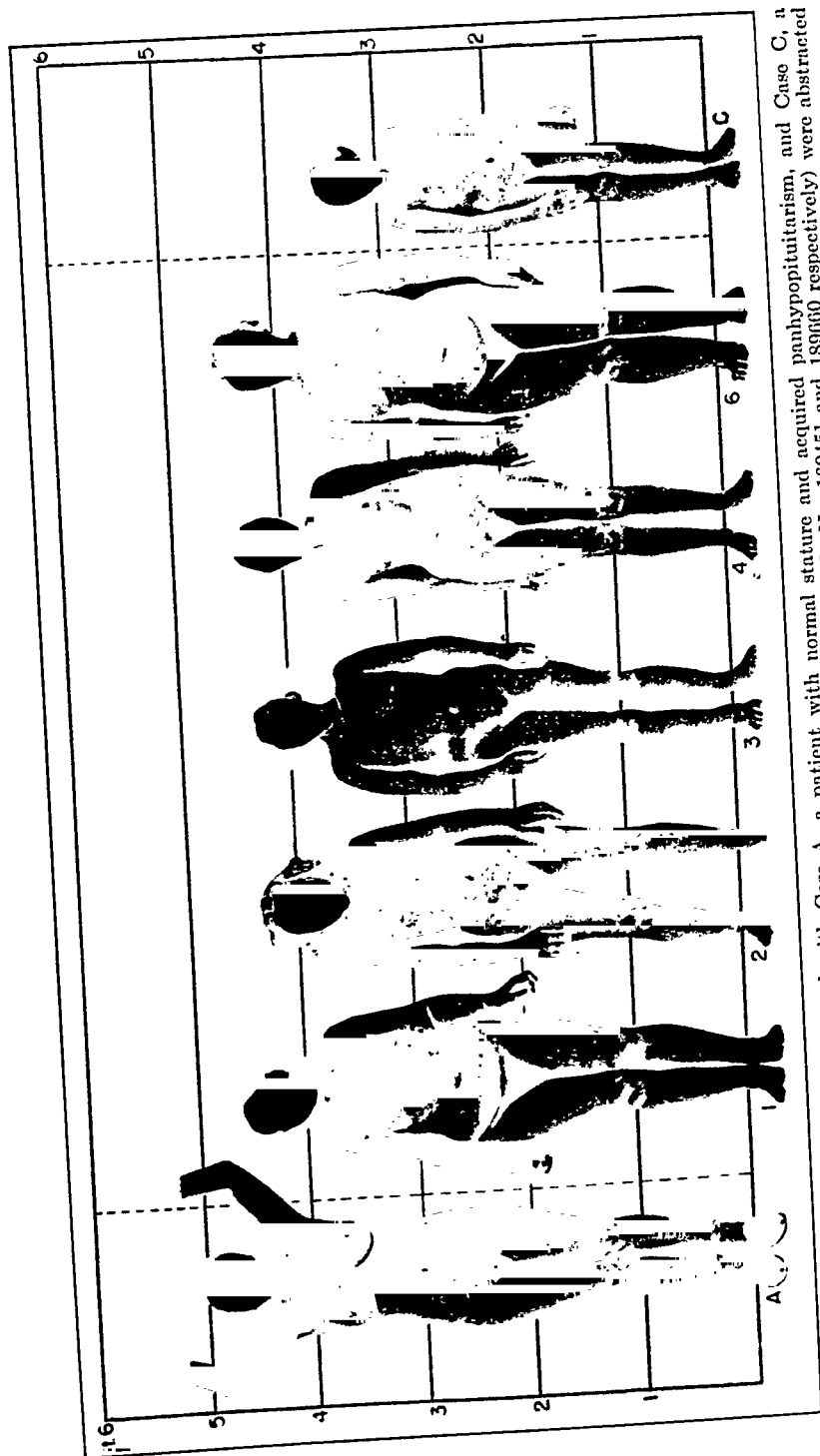


FIG. 1.—Cases 1, 2, 3, 4 and 6 compared with Case A, a patient with normal stature and acquired panhypopituitarism, and Case C, a patient with congenital panhypopituitarism. Case histories of Cases A and C (M. G. H., No. 160451 and 189660 respectively) were abstracted in a previous publication.¹ The breast development and large amount of pubic hair of Cases 1 and 4 are the result of estrin therapy.

The picture was further complicated by the development of grand mal seizures at the age of 28. These brought up the question of hypoglycemia, which is so often found in conjunction with panhypopituitarism. Her basal metabolic rate tended to be low, about -13% . Her serum calcium was 11.5 mg. per 100 cc.; her serum phosphorus 4.3 mg. per 100 cc. A Roentgen ray of her spine showed deformities in many of the vertebrae and some wedging, interpreted as "epiphysitis" (cf. Case 3).

The patient entered the hospital again in 1940 because of a detached retina resulting from a grand mal seizure. The correct diagnosis was then arrived at, when it was found in the insulin tolerance test that she was not hypoglycemia unresponsive, when the FSH test turned out to be positive for 10 mouse units per 100 cc., and when the 17-ketosteroid assays showed values in the neighborhood of 2 and 3.2 mg. per 24 hours. Roentgen ray films taken at the age of 29 and again at the age of 39 showed union of all epiphyses except the crest of the ilium which was not united even at the age of 39. The serum cholesterol was 197 mg. per 100 cc.

CASE 5. E. C., No. 47830, was first seen at the age of 16 because she had never menstruated. She did not know when growth had become retarded. She had been a full term baby weighing only 4 pounds at birth and had always been sickly. Other members of her family were normal in height. She had developed a small amount of pubic hair at the age of 14.

On physical examination at the age of 21 (see Fig. 3) she was poorly developed and nourished; her height was 4 feet $7\frac{1}{2}$ inches with her span 10.7 cm. greater than her height; her weight was 76 pounds. Her breasts were not developed at all and the external genitalia were infantile; the uterus was not made out by rectal examination; there was a small amount of pubic hair. The blood pressure was always elevated, circa 150/110; there was no other evidence of coarctation of the aorta, however.

She was operated upon at the age of 23 for intestinal obstruction from adhesions. A small amount of fluid was found in her peritoneal cavity at that time. Her uterus was found to be very small, cervix being two or three times the size of the fundus; the ovaries were present but less than $1 \times 0.3 \times 0.3$ cm.

Roentgen ray films at age of 20 showed at least 5 years delay in bone age; at 26 they showed union of all epiphyses except those of vertebrae. The FSH test for 10 mouse units per 100 cc. of urine was repeatedly positive.

During October, 1937, the patient was started on large doses of estrin therapy (circa 1.5 mg. of estradiol benzoate intramuscularly twice weekly with intervals without therapy to allow for estrin-withdrawal bleeding). It was noted that her strength and weight increased during this therapy and receded when the therapy was omitted. She developed a large amount of axillary and pubic hair and considerable breast development (see Fig. 3). The 17-ketosteroid assays varied from 1 to 3.3 mg. per 24 hours after 2 years of large doses of estrin; after an additional $1\frac{1}{2}$ years of large doses of estrin and progestin therapy these values rose to a range of about 8 to 11 mg. per 24 hours. With the addition of progestin therapy starting July, 1940, there was a further increase in her well-being.

CASE 6. M. K., No. 144936, was first seen in 1938 at the age of 28. She had never had a menstrual period and had not developed sexually; she had been born at full term and had always been stocky in build. She believed that pubic hair had developed between the ages of 12 and 16. Other members of the family tended to be of short stature.

On physical examination she was 4 feet 7 inches with a span 7 cm. greater than her height; she weighed 146 pounds and was very sturdy (see Fig. 1). She had a slight amount of pubic hair and practically no axillary hair; her breasts resembled those of a girl in adolescence and consisted mostly of fatty tissue; external genitalia were infantile; cervix was very small as felt per rectum. Blood pressure was 134/86.

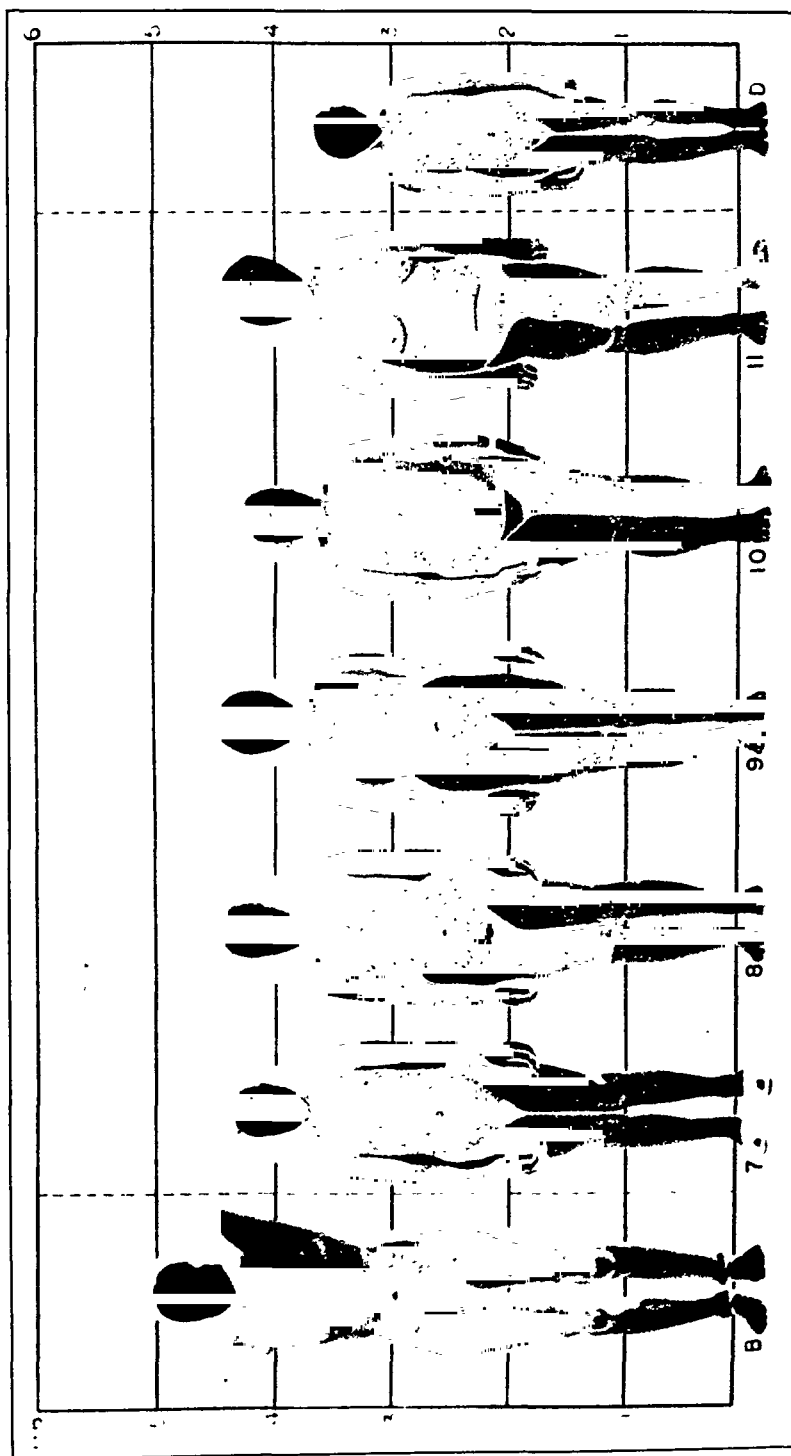


FIG. 2.—Cases 7, 8, 9, 10 and 11 compared with Case B with Addison's disease and complete absence of axillary and pubic hair (see text) and Case D (M. G. H., No. 210582) with congenital panhypopituitarism. The apparent breast development in Case 11 is due to fat deposits and not to breast tissue.

Several FSH tests for 10 mouse units per 100 cc. of urine were positive; two 17-ketosteroid assays were 5.1 and 4.5 mg. per 24 hours respectively. The Roentgen ray films of the bones taken at the age of 28 showed union of all the epiphyses. An insulin tolerance test was not abnormal. Two basal metabolic rates were +3% and +15% respectively. On peritoneoscopic examination the uterus was found to be infantile; the right tube was seen, but nothing but the slightest amount of tissue was seen in the region of the ovary; on the left side neither tube nor ovary was seen.

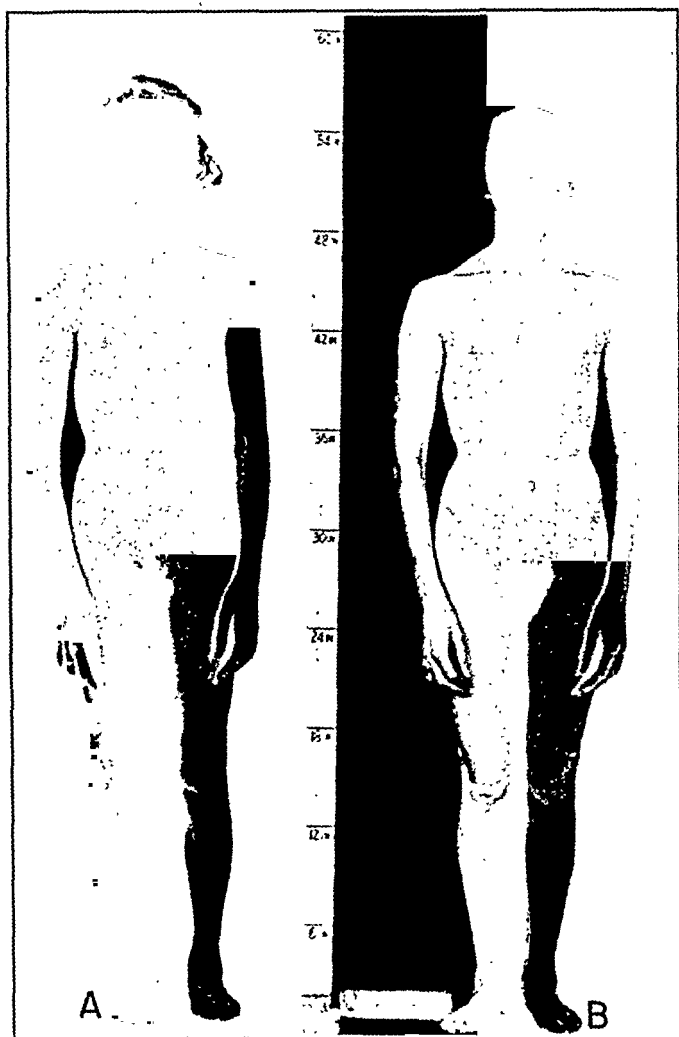


FIG. 3.—Case 5 before estrin therapy (A) and after estrin therapy (B). Note marked increase in pubic hair; note also increase in breast development which was more marked than suggested by the photograph.

CASE 7.—J. C., No. 296226, was first seen at the hospital in 1941 at the age of 14. Retarded growth had first been noted at the age of 8. At the age of 10 she had undergone an operation at the Children's Hospital in Boston for bilateral congenital webbing of the neck. Between November, 1938, and September, 1939, she had been treated with small doses of thyroid ($\frac{1}{2}$ to $\frac{3}{4}$ gr. daily) at the Children's Hospital; larger doses had led to symptoms of toxicity; during that time she had gained $1\frac{1}{4}$ inches in height

and 5 pounds in weight. Other members of the family were of normal stature.

On physical examination she was 4 feet 5 inches, with a span 1 cm. greater than her height; she weighed 71 pounds and was very sturdy (see Fig. 2). There was no breast development; the external genitalia were infantile; there was a small amount of pubic hair and no axillary hair. She showed scars on either side of the neck where the webbing had been removed; there was a marked increase in the "carrying angle" of the arm (*vide infra* [Fig. 4]). She had moderate hypertension, 146/88, which led to the suspicion on the part of our colleague Dr. William Parson of coarctation of the aorta. This was confirmed by Roentgen ray examination.

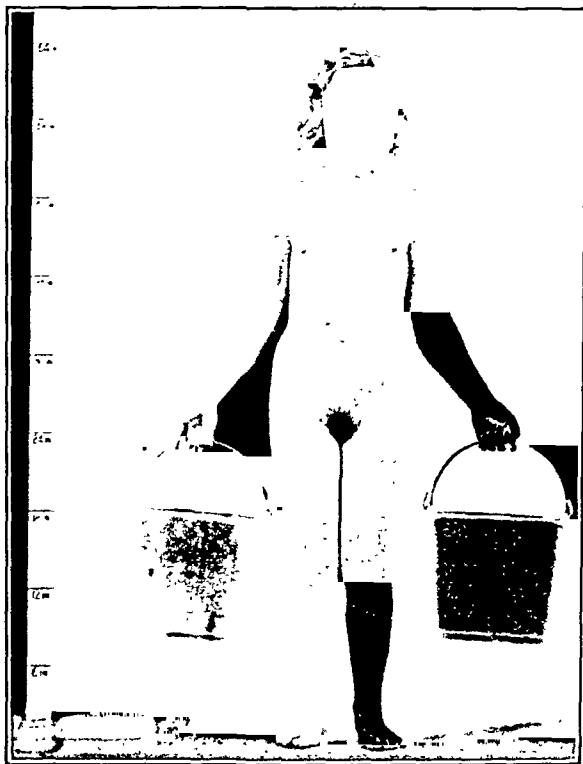


FIG. 4.—Photograph of Case 7 with Turner's syndrome to illustrate increase in "carrying angles" of arms.

Her bone age showed only slight retardation—greater than 1 year and less than 2 years. An FSH test for 10 mouse units per 100 cc. was positive; two 17-ketosteroid assays were 4.8 and 5.1 mg. per 24 hours respectively. The serum calcium was 11.6 mg. per 100 cc.; serum phosphorus 5 mg. per 100 cc.; serum phosphatase 6.4 Bodansky units.

CASE 8. A. G., No. 323961, was first seen at the hospital in 1941 at the age of 18½ years. (The authors wish to thank Dr. Z. Eileen Taylor for permission to study and report this patient.) Except that she had weighed only 4 pounds at birth her history until the age of 10½ was irrelevant. At that time she had suffered from a severe mastoiditis and bilateral otitis

media which had necessitated her being in bed 3 months. Following this illness her growth had become retarded; although she already had a slight amount of axillary and pubic hair at the age of 10½, further sexual development had not occurred; hot flashes had been noted for a short time following this. Her breasts had developed slightly under estrin therapy at the age of 16; she had also received a variety of other endocrine preparations without any marked benefit.

On physical examination she was short, 4 feet 7½ inches, with a span 1.1 cm. greater than her height; she was sturdy (see Fig. 2); there was almost no breast development but moderate amounts of axillary and pubic hair. As in Case 3 there was an increase in the "carrying angles" of the arms. Her blood pressure was 128/80. External genitalia were infantile. Roentgen ray films showed that her bone age was more than 3 and less than 5 years retarded. An FSH test for 10 mouse units per 100 cc. of urine was positive; two 17-ketosteroid assays were 4.8 and 5.1 mg. per 24 hours respectively.

CASE 9. Rh. F., was referred to one of us by Dr. Norman Popkin of Springfield, Mass., in November, 1941, at the age of 20 years. She had always been somewhat short, though otherwise well in childhood, and had not considered herself abnormal until the age of 15 when she had failed to menstruate. At that time she had been seen at the Evans Memorial Hospital where she had been given "pituitary tablets" and some injections. She had been again admitted in July, 1940, and had been discharged with the diagnosis of hypoplasia of the uterus, dwarfism, hypopituitarism and with the recommendation that she be given estrin therapy. This had been started in November, 1940, and had been followed by a certain amount of uterine bleeding and increased development of the breasts. Since November, 1940, she had been taking 1½ gr. of thyroid daily, and since February, 1941, 3 gr. daily.

On physical examination she was 4 feet 9½ inches with a span 2.9 cm. greater than her height and like Cases 7 and 8 an increase in the "carrying angles" of her arms. Her weight was 112 pounds. She was sturdy (see Fig. 2); had well-developed axillary and pubic hair and slight breast development (see estrin therapy); external genitalia were poorly developed and uterus as felt by rectum was very small. She had an external squint of the left eye. Blood pressure was 140/90 without other evidence of coarctation. Roentgen ray films showed a retardation of bone age of greater than 2 years and less than 4 years. Roentgen rays of the spine showed moderate osteoporosis and rather marked "epiphysitis" (see Fig. 5). An FSH test was positive for 10 mouse units per 100 cc. of urine and negative for 30 mouse units. Two 17-ketosteroid assays were 4.3 and 3 mg. per 24 hours respectively. The serum calcium was 12.5 mg. per 100 cc.; serum phosphorus, 3 mg. per 100 cc.; serum phosphatase, 5.6 Bodansky units. Repeat values were 11.1 mg. per 100 cc., 3.8 mg. per 100 cc. and 3.9 Bodansky units respectively. A 24-hour calcium excretion in the urine on a low-calcium diet was perfectly normal—61 mg.

CASE 10. H. M., No. 329326, was first seen at this hospital in 1941 at the age of 37 years complaining of bilateral cataracts. She had always tended to be short; her breasts had never developed; she had never menstruated. She probably had had a cleft palate for which she had been operated on at the age of 10 years. She thought that she had not grown since that time. The cataracts had been present for 2 years. There was no family history of short stature, two brothers being over 6 feet. On physical examination she was 4 feet 8¼ inches with a span 2.5 cm. greater than her height. She weighed 128½ pounds. She was well nourished (see Fig. 2) and looked at least 20 years older than she actually was. Thus, the skin on her face was slightly wrinkled and atrophic and she was

losing the hair on the top of her head (see Fig. 6). She had bilateral cataracts and well-developed Heberden's nodes (see Fig. 7). Blood pressure was 134/90. There was absolutely no breast development. External genitalia were infantile; she had practically no axillary hair and rather scanty pubic hair. Pelvic examination showed infantile organs but a slightly enlarged clitoris.

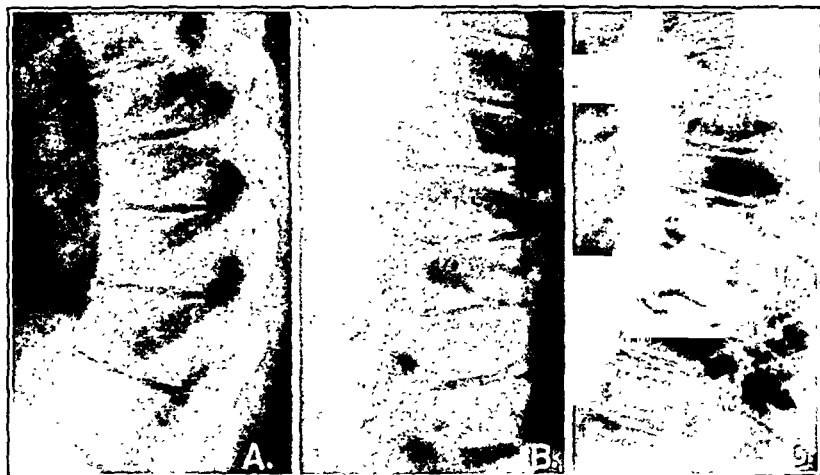


FIG. 5.—Illustration showing so-called "epiphysitis." A, Case 4. B, Case 9. C, Case 11.



FIG. 6.—Illustrations to show tendency of patients to exhibit senility. A, Case 4, age 40; B, Case 10, age 37; C, Case 11, age 30.

An FSH test for 50 mouse units per 100 cc. of urine was positive. Two 17-ketosteroid urinary assays were 4.9 and 6.6 mg. per 24 hours respectively. Roentgen rays showed closure of all epiphyses. There was generalized osteoporosis and considerable dorsal kyphosis with marked irregularity of the surfaces of the dorsal vertebræ, especially their anterior halves, and with considerable diminution in the depths of the vertebræ (see Fig. 5). Roentgen ray films of the elbows showed a peculiar underdevelopment of the external condyles of the humeri (see Fig. 7).

CASE 11.—J. A. M., No. 334333, was referred to this hospital in 1941 at the age of 30 by Dr. Vera Kinsey, with the diagnosis of diabetes mellitus and primary ovarian insufficiency. She had ceased growing at 12 and had never had a menstrual period; pubic hair had developed 2 years previously and axillary hair $1\frac{1}{2}$ years previously. Diabetes had first been diagnosed at the New England Hospital for Women in November, 1941. She had had all the classical symptoms including polyuria, polydypsia and pruritus vulvæ; her initial fasting blood sugar had been 171 mg. per 100 cc.; she had responded well to insulin. During the past year she had developed unconscious episodes, in some of which she had hurt herself. There was no family history of short stature. The patient had been married for 12 years but had never become pregnant.

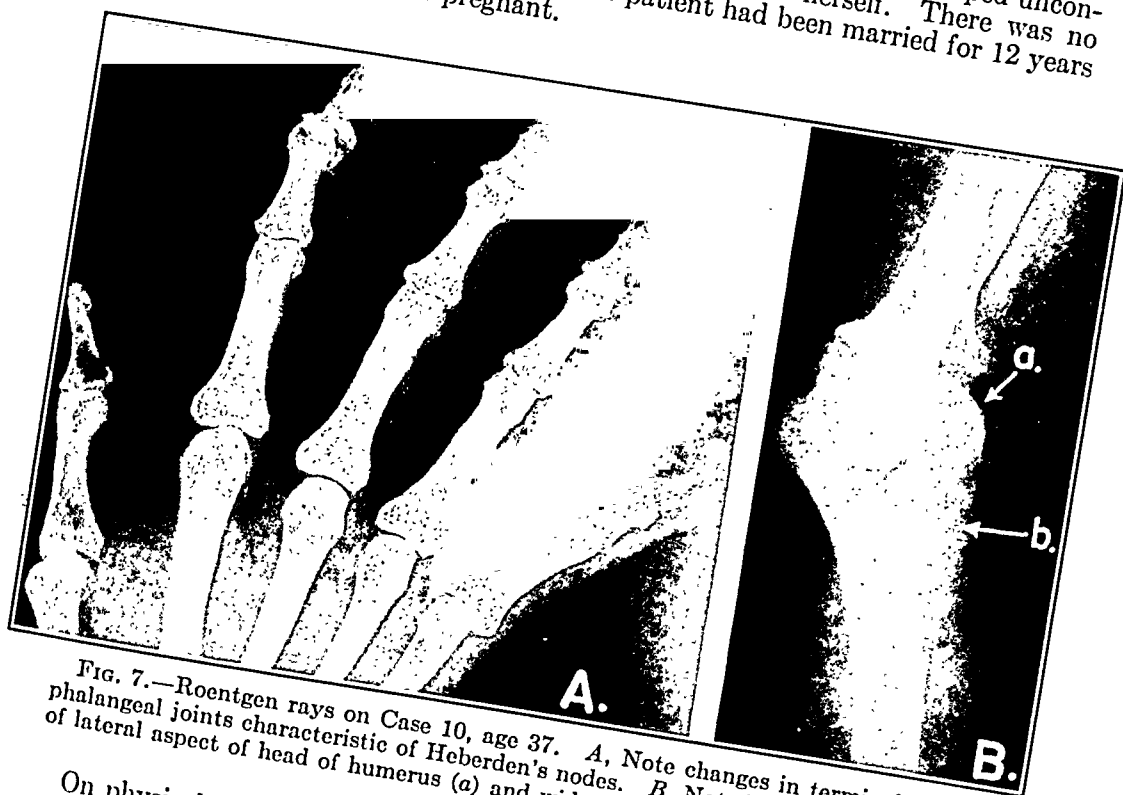


Fig. 7.—Roentgen rays on Case 10, age 37. A, Note changes in terminal interphalangeal joints characteristic of Heberden's nodes. B, Note lack of development of lateral aspect of head of humerus (a) and widening of humerus just above (b).

On physical examination the patient was 4 feet $8\frac{1}{2}$ inches in height with a span 5.9 cm. greater than the height, and weighed $159\frac{3}{4}$ pounds. She was very obese; there was no breast tissue palpable, although at first sight because of large amounts of fat she appeared to have well-developed breasts (see Fig. 2). External genitalia were infantile; there was a small amount of axillary and pubic hair. Her facial appearance was that of a much older woman and the hair on the top of her head was beginning to thin out (cf. Case 10). Blood pressure was 136/100; there was no other evidence of coarctation of the aorta.

The FSH test for 10 mouse units per 100 cc. of urine was positive. Two 17-ketosteroid assays showed 0.6 and 2.7 mg. per 24 hours respectively.

Review of the Literature. Many features of the syndrome under discussion, exclusive to be sure of the important laboratory tests which assist in making the diagnosis *in vivo*, have been quite adequately set forth in the German pathologic literature. Olivet,²⁹ in

1923, reported an autopsied case with congenital absence of the ovaries. He emphasized the small stature (148 cm.) and the presence of axillary and pubic hair, in spite of absence of other secondary sex development. Pich,³² in 1936, summarized the literature to that date and added 2 (Cases 1 and 3) interesting cases. Of the cases which were cited by Pich exclusive of Olivet's case, the authors feel that only four^{33,34,35,36} surely belong to the syndrome in question. In the absence of the laboratory tests it is obviously difficult to separate this syndrome from certain other conditions.

As to diagnosis *in vivo*, mention of the syndrome was made in a previous paper from this clinic¹⁵ before the references in the German literature had been found. Varney, Kenyon and Koch⁴⁸ independently recognized the syndrome and reported on several cases in May, 1941, and very kindly invited the authors to present their cases in the discussion. This was done by one of us (P. H. S.). The cases of the Chicago group were later reported;⁴⁹ the first 2 undoubtedly belong to the syndrome under discussion, the second 2 in all likelihood represent examples of decreased rather than absent ovarian function. These authors also called attention to another case published by Tronci.⁴⁶

Discussion. Decreased Stature. One of the most surprising features of the syndrome under discussion is the decreased stature. These patients, however, can hardly be called dwarfs. Pich³² emphasized this point and applied the word "Minderwuchs" (decreased stature) as opposed to "Zwergwuchs" (dwarfism); unfortunately the English language does not have one word for the translation of "Minderwuchs." One rather extraordinary feature about the decreased stature is the marked uniformity in size that these patients exhibit. The heights in the 11 cases here reported varied from 4 feet 5 inches to 4 feet 9½ inches (average, 4 feet 7 inches). Furthermore, the shortest patient in the series, who was 1 inch shorter than any of the other patients, has not yet attained her full height; the tallest patient in the series is 1 inch taller than any of the other patients.

The exact cause of the decreased stature remains problematical. In the final analysis the height which a person reaches depends on two factors: (a) the rate of growth, and (b) the length of time during which the individual grows. In this condition, since there is a delayed union of the epiphyses and hence an increase in the time during which the patients grow, the disturbance is obviously in the rate of growth.

There are five possibilities which seem worth discussing in regard to the cause for the decreased rate of growth.

The first possibility is that estrin may have a direct effect on the rate of growth in the epiphyseal cartilage. Estrin does cause proliferation of cells in many tissues; furthermore, there is a marked propensity for atrophy of tissue after the menopause (*cf.* postmenopausal osteoporosis and atrophy of the skin³). Zondek,⁵³ on

the other hand, produced dwarfism in animals by large doses of estrin. To be sure the *modus operandi* there was presumably an inhibiting action on the anterior pituitary; but, had there been any direct effect of estrin on the epiphyseal cartilages, one would have expected to have seen a temporary spurt of growth. Bogart, Sperling, Barnes and Asdell,⁷ moreover, found that oöphorectomized rats grow more rapidly than normal female rats. Furthermore, in that syndrome discussed below, where estrin is equally diminished but where the primary fault is a lack of gonadotropic hormone production in the anterior pituitary in the absence of other pituitary insufficiency, one finds normal heights. We think it is unlikely that changes in growth are due to a direct effect of estrin on the epiphyseal cartilage.

The second possibility is that a primary ovarian deficiency leads to secondary changes in the anterior pituitary which in turn interfere with the production of growth hormone by said gland. Thus it is possible that a gland which is producing a large amount of FSH might be less able to produce growth hormone. The autopsy cases summarized by Pich³² did show minor changes in the histology of the anterior pituitaries, some cases showing an increase in the eosinophil cells and some an increase in the chromophobe cells. Against this hypothesis is the fact that castration in males does not lead to decreased stature in spite of the fact that the same overproduction of FSH in the pituitary takes place. The authors do not favor this explanation of the decreased stature.

A third possibility is that the decrease in estrin production leads to a secondary change in the adrenal cortex which in turn results in a decreased growth rate. There are many pieces of circumstantial evidence which rather lead the authors to favor this point of view. In the first place, testosterone is an important growth hormone; the adrenal cortex produces some steroids very similar to testosterone; tumors of the adrenal cortex lead not only to sexual precocity but to marked somatic precocity; ergo, anything that might affect adrenal cortical function might affect growth. Secondly, there is a marked spurt in growth in adolescent females at the time of puberty; concomitantly the 17-ketosteroid excretion in the urine, which is an index of adrenal cortical function, rises. Thirdly, in the condition under discussion associated with decreased stature the 17-ketosteroid excretion remains at about the level found in the prepuberty normal individual, suggesting that there is a decrease in adrenal cortical function as compared with the normal. Fourthly, there is considerable evidence that estrin stimulates some hormone of the anterior pituitary which in turn stimulates the adrenal cortex. Indeed, the authors attribute the rise in 17-ketosteroid production in females at puberty to this interrelationship. A hypothetical diagram illustrating the above-mentioned relationships is presented in Figure 8 and discussed below under "Pathologic Physiology."

A fourth possibility was suggested by Pich,³² namely that the decreased stature was due to an associated thymus insufficiency. In her first 2 cases with marked decrease in stature she found marked involution of the thymus, whereas in the third case where there was less decrease in stature the thymus was normal. We have no comments to make on this hypothesis.

A fifth possibility is that the decreased stature has nothing to do with the ovarian hypofunction but that both are the result of some widespread defect in the organism. The frequency with which other congenital anomalies are met with in this condition would be a point in favor of this hypothesis.

The data to date are suggestive that estrin therapy accelerates growth in this condition; thus Case 7 grew 1 inch in 6 months under estrin therapy, whereas during the previous $2\frac{2}{3}$ years she had grown 3 inches. If it can be established that estrin does stimulate growth, possibilities 4 and 5 enumerated above could be eliminated.

Bone Age. All our patients showed evidence of delayed union of the epiphyses and most exhibited eunuchoid proportions, i. e., the long bones were out of proportion to the rest of the body. Thus the span in each instance was greater than the height. The normal individual of average height, of course, tends to have a span which is equal to his height; the normal individual of short stature tends to have a span which is less than his height. Therefore, when one finds a short individual with a span greater than the height, it is strong evidence that the epiphyses were late in closing.

There is considerable individual variation in this group as regards bone age. In most instances, however, the retardation was not so great as one sees in pituitary dwarfism. Thus, in 5 patients (D. W. S., age 28; M. K., age 28; H. M., age 37; U. H., age 39; J. A. M., age 30) the epiphyses were closed; this statement does not apply to the crest of the ilium which was noted to be still open in patient U. H. at the age of 39. C. M. at the age of 22 showed the greatest retardation of the patients in our group; thus her bone age was estimated to show a retardation of greater than 7 years and less than 8 years. J. C., on the other hand, at the age of 14, had a bone age which showed a retardation of more than 1 year and less than 2 years. The patient of Roessl and Wallart³⁵ had open epiphyses at 39.

Just why the epiphyses should be less delayed in closing in ovarian insufficiency as opposed to panhypopituitarism is not clear; but it may very well be connected with the fact that the ovarian cases have normal or potentially normal adrenals, whereas the pituitary dwarfs have hypoplastic adrenals.

Patients With Primary Ovarian Insufficiency and Primary Amenorrhea but Without Short Stature. One does encounter instances (2 cases in our Ovarian Dysfunction Clinic) where a patient has never had a period (so-called "primary amenorrhea") and has little or no breast development, where the FSH test is persistently posi-

tive for at least 10 mouse units per 100 cc. of urine, but where one does not encounter short stature. Some of these cases, if not all of them, especially where there is slight breast development, may be explainable on the basis of a "premenarchal menopause præcox." Thus, the menopause may occur at any age; in some instances it occurs just after the menarche; there is no reason to believe that it might not occur just before puberty. If such were the case one might have a normal premenarchal adolescence with normal growth; ovarian failure might then take place at about the time the periods were to be established. This would lead to non-union of the epiphyses; the net result might even be slightly increased growth.

The above explanation is not very satisfactory for those cases where there is absolutely no breast development. The normal female adolescent child has considerable breast development several years before the establishment of the menarche.

Pich³² correlated the relatively normal size (156 cm.) of her third case with the fact that the thymus was not as atrophied as in most cases. This is a possible explanation.

If one believes, as the authors rather do, that the short stature is related to a slight accompanying underfunction of the adrenal cortex, one might hypothesize that in certain cases this underfunction does not take place. It is of some interest that the 2 cases without short stature had slightly higher, albeit not significantly higher, 17-ketosteroid assays (5.3 and 4.7 mg. per 24 hours in 1 case; 7.5 and 5 mg. per 24 hours in the other) than 10 of the 11 cases of short stature (range: 1 to 5.1 mg.; average, 3.8 mg. per 24 hours*). The 17-ketosteroid excretions on Case 10, however, were 4.9 and 6.6 mg. per 24 hours. Finally, both the cases without decreased stature had more axillary and pubic hair than most of the untreated ones with short stature. Since this hair is probably an indication of adrenal cortical function (*vide infra*) this finding would point in the same direction.

Axillary and Pubic Hair. As stated above, the patients with the syndrome under discussion tend to have small amounts of axillary and pubic hair as opposed to pituitary dwarfs in which such hair is entirely absent. This brings up the question as to what is the direct cause of such hair growth in females. The fact that it grows out during puberty has led to the assumption that it is directly due to some ovarian hormone. If such were the case it is difficult to see why the patients with primary ovarian failure should have any such hair growth at all. The authors rather believe that the immediate hormone which stimulates growth of hair in these regions comes from the adrenal cortex.

In favor of this thesis that axillary and pubic hair are due to

* One value of 15.3 mg. per 24 hours was discarded on Case S as almost surely wrong.

adrenal cortical rather than ovarian function are the following considerations:

1. The 17-ketosteroid excretion, which is an index in females of adrenal cortical function,¹⁵ rises at puberty, showing that there is a change in the function of the adrenal cortex as well as of the ovaries at that time; therefore, *a priori*, changes at that time might just as well be attributed to adrenal cortical function as to ovarian function.

2. Pituitary dwarfs have no axillary or pubic hair (see Figs. 1 and 2), whereas the patients with the syndrome under discussion usually have moderate amounts; the adrenal cortices in the former cases are atrophied, in the latter they are relatively normal.

3. Patients with the syndrome have less than the normal amount of axillary and pubic hair; the 17-ketosteroid excretion in these patients, while present, is subnormal.

4. There are four conditions in women which lead to loss of axillary and pubic hair; these four conditions are panhypopituitarism or Simmonds' disease, Addison's disease, hypothyroidism, and extreme old age; the 17-ketosteroid excretions are extremely low or absent in all four of these conditions.¹⁵

5. The authors have quite clear evidence that testosterone has a direct effect on axillary and pubic hair; since the adrenal cortex produces a hormone very similar to testosterone, if not testosterone itself, this is another reason to believe that the adrenal cortex effects axillary and pubic hair growth.

6. That ovarian function *per se* is not important to the maintenance of axillary and pubic hair is the fact that there is very little change after normal or artificial menopause in its growth.

7. Castration in adult males leads to a diminution of pubic hair toward the configuration of that seen in normal females; the axillary hair diminishes but usually does not disappear; prepuberty castration in males does not prevent the development of axillary and pubic hair which reaches a degree not dissimilar to that seen in normal females; since the castrated male still has a normal adrenal cortex, the above findings are consistent with the hypothesis under discussion.

8. The authors have studied a patient with Addison's disease who underwent a normal menarche with regular periods but who never developed any axillary or pubic hair (see Fig. 2, Case B). Her history is abstracted below under "Case B."

9. Estrin therapy to pituitary dwarfs has no effect on the status of axillary and pubic hair; with the same therapy to patients with the syndrome under discussion there is a marked increase in axillary and pubic hair; since estrin therapy is thought to stimulate the adrenal cortex *via* the pituitary these observations become explicable.

On the other hand, it is of interest that in many of these cases development of axillary and pubic hair occurs at about the time for

normal puberty; in some instances its appearance is distinctly retarded; in Case 11 it did not appear until the age of 28. The development of axillary and pubic hair at about the normal time for puberty in these cases suggests that the factor which normally sets off the stimulation of the ovaries by the pituitary at puberty leads at the same time to stimulation of the adrenals by the pituitary; in the condition under discussion because of lack of the ovaries one sees only the adrenal component. These observations in themselves would suggest that the increase in adrenal activity at puberty was not dependent on estrin production.

Addison's Disease With Absence of Axillary and Pubic Hair. CASE B (see Fig. 2). H. M., No. 210582, was first seen at this hospital in 1939 at the age of 21 years. She presented the classical picture of Addison's disease with pigmentation, hypotension, low serum sodium and chloride, hypoglycemia unresponsiveness as shown by the insulin tolerance test, and absence of 17-ketosteroids in the urine. Addison's disease had been present for at least a year and probably longer as "she had always been weak."

Her periods began at the age of 16 years and stopped 1 year before admission. She had never developed any axillary or pubic hair (see Fig. 2), in spite of the fact that she was well developed otherwise. Height was 5 feet 1 inch.

Other Congenital Anomalies. Pich³² called attention to the frequency with which other congenital anomalies are met with in this syndrome. In this connection it is very interesting that her Case 3 had a coarctation of the aorta as did our Case 7. This latter patient also had congenital webbing of the neck for which she was operated upon at the Children's Hospital.²⁴ It is of further interest that a patient recently reported by Ornstein³⁰ as a case of hypopituitarism also had coarctation of the aorta; from the data published the authors feel that there is little doubt that the diagnosis was primary hypoövarianism rather than hypopituitarism. Dr. Lawson Wilkins (Johns Hopkins Hospital) showed one of the authors a patient who in all respects fits the syndrome and who like Case 7 has both coarctation of the aorta and webbing of the neck. He called the authors' attention to "Turner's syndrome."⁴⁷ This latter author described 6 cases in women characterized by short stature, complete absence of breast development, in most instances slight amounts of axillary and pubic hair, congenital webbing of the neck, and increase in the carrying angles of the arms (cubitus valgus) (see Fig. 4). Unfortunately, there were no studies on excretion of follicle-stimulating-hormone, nor any data on which to base the presence or absence of coarctation of the aorta. Strong evidence that Turner's syndrome is due to ovarian insufficiency and not to panhypopituitarism was brought forth by E. P. Sharpey-Shafer.⁴³ He reported on the autopsy findings of a case which died of miliary tuberculosis. The endocrine glands, except the ovaries, showed no gross lesions. One ovary could not be found and the other was thought to have been destroyed by tuberculosis, as no active ovarian tissue was demon-

strated. No mention was made of the aorta. Two of Turner's cases had internal squints as did our Case 9. Case 11 in our series had had a cleft palate; Case 10 had an anomalous condition of the bones at the elbow (see Fig. 7).

Ovarian Pathologic Anatomy. From the German literature, summarized by Pich,³² it is quite clear that most of these cases are suffering from a congenital absence or extreme malformation of the ovaries. Less often the ovarian lack may be due to inflammatory disease at an early age. In Case 1 the question was raised, but not verified, that the ovarian lack might have been the result of destruction of the ovaries by Malta fever. Case 5 in our series showed rudimentary ovaries on gross inspection during an operation for appendicitis; they were reported as being less than $1.3 \times 0.3 \times 0.3$ cm. in size. Cases 3 and 6 were examined with a peritoneoscope without finding any definite ovarian tissue. In those cases where there is a coarctation of the aorta it seems possible that the ovarian insufficiency may in some way be connected with faulty blood supply.

Precocious Senility. From an academic point of view one of the more interesting features of this weird syndrome is the marked tendency to precocious senility reminiscent of that seen in panhypopituitary dwarfs where the term "progeria" has been applied. In a previous communication from this laboratory³ attention has been called to the marked tendency of women after the menopause to develop osteoporosis and atrophy of the skin. It would now appear that ovarian lack largely accelerates the aging process of atrophy in general; thus a patient of 30 with primary ovarian insufficiency may look almost as old as a woman 30 years after the menopause.

Our series contains 4 patients over 30 years, Cases 4, 6, 10 and 11, aged 40, 31, 37 and 30 respectively. All showed atrophy of the skin of the face and wrinkles similar to those seen in much older women (see Fig. 6). Case 10, furthermore, had senile cataracts, marked alopecia of the scalp and Heberden's nodes (see Fig. 7). Case 11 had mild diabetes similar to that seen in older women. Both Cases 4 and 10 had developed epileptic seizures, the exact significance of which is not apparent.

What effect estrin therapy will have on the premature aging remains problematical; it will undoubtedly inhibit its development; will it make it retrogress?

Osteoporosis and "Epiphysitis" of Spine. Several of the patients in this group have shown moderate osteoporosis especially of the spine and pelvis. When present it is very reminiscent of that seen in the postmenopausal state³ and undoubtedly due to the same cause, namely ovarian insufficiency.

Many of the cases, notably Cases 3, 4, 9, 10 and 11, showed to a greater or lesser degree irregularities, locally termed "epiphysitis,"

on the upper and lower margins of the vertebræ (see Fig. 5). The exact nature of these changes remains obscure.

Pathologic Physiology. In this section an attempt will be made to elucidate the deranged endocrine pattern in the syndrome under discussion. Certain parts of this pattern are very clear; others are still most hypothetical. In Figure 8, *A* a tentative scheme of the normal interrelationships of certain hormones which pertain to the problem at hand is depicted; in Figure 8, *B* certain hypothetical alterations in these interrelationships in the syndrome under dis-

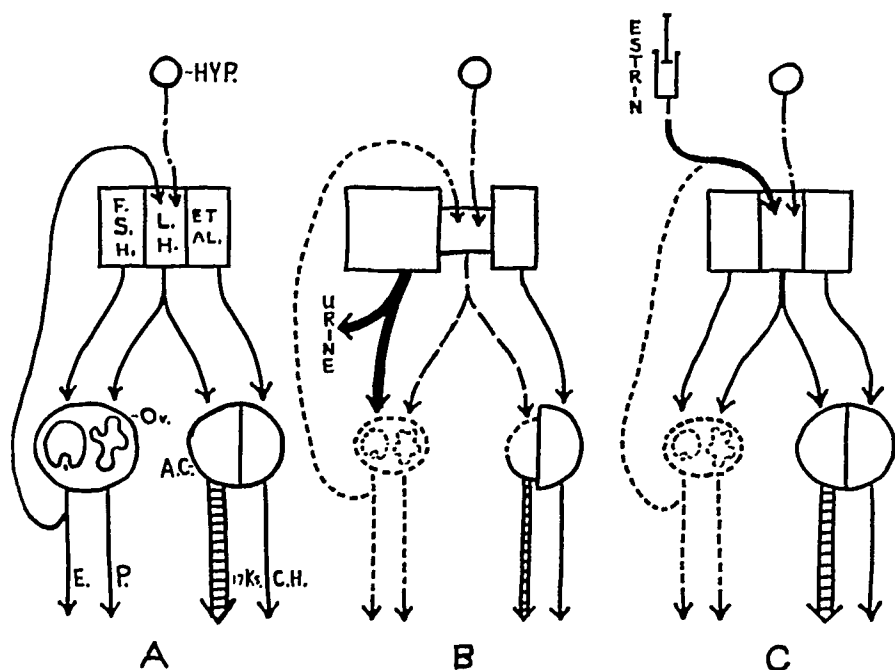


FIG. 8.—Hypothetical and schematic diagram illustrating possible hormonal interrelationships in (A) normal status, (B) condition under discussion, and (C) the condition under discussion under estrin therapy. The pituitary is divided into three compartments, that making follicle-stimulating hormone (FSH), that making lutening hormone (LH), and that making all the rest of the hormones, here designated "et al." Ov., ovary; E, estrin; P, progesterone; A.C., adrenal cortex; C.H., adrenocortical hormones which are not 17-ketosteroids; 17-KS, 17-ketosteroids made from adrenal cortex; HYP., hypothalamus. Dot-dash line connecting hypothalamus with pituitary indicates hypothalamic-pituitary nervous pathway partly controlling pituitary function. For further discussion see text.

cussion are set forth; finally in Figure 8, *C* a possible effect of estrin therapy on this hormonal imbalance is shown. The authors present these diagrams, not that they have much hope that they are correct in all their ramifications, but as a first approximation; it is hoped that others will make corrections.

That there is primary ovarian insufficiency in this syndrome there is little doubt. Thus, the autopsy findings in the German literature³² and the high excretions of follicle-stimulating-hormone are strong evidence in this direction.² Furthermore, the low 17-keto-

steroid excretions make it quite certain that there is an accompanying disorder of the adrenal cortex.¹⁵

There is considerable evidence^{9,12,13,16,19,20,23,26,39,50} that estrin stimulates either the luteinizing hormone (LH) of the anterior pituitary (see Fig. 8, A) or a closely related hormone (*vide infra*); there is also evidence that estrin administration causes hyperplasia of the adrenal cortex in female rats³⁹ and hyperplasia of the androgenic zones in male mice;^{8,22} one is tempted, therefore, to hypothesize that the effect of estrin on the adrenal cortex is mediated through the LH function of the anterior pituitary (see Fig. 8, A). That LH does stimulate the adrenal cortex is further suggested by the fact that testosterone and progesterone, two substances that almost surely inhibit LH production since they are the end results of LH production, both cause atrophy of the adrenal cortex.^{21,27,37,38,40,45,50} There is positive as well as this theoretical evidence that testosterone inhibits LH;^{31,41,52} there is also such evidence for progesterone.^{6,10,25} The production of adrenal cortical hyperplasias and tumors in both male and female animals by gonadectomy^{11,17,41} suggests that the sequence of events in such experiments may be: *a*, gonadectomy; *b*, increase of LH production; and, *c*, adrenal cortical stimulation.

From the above observations one would like to attribute the adrenal cortical hypofunction in the syndrome under discussion to lack of LH stimulation and this in turn to lack of estrin. Such an interrelationship is supported by the observation that estrin therapy in these individuals leads to the production of axillary and pubic hair, a phenomenon probably linked with adrenocortical function (*vide supra*). The authors regret that they do not have unequivocal evidence that estrin therapy also leads to an increase in 17-ketosteroid excretion.

Before leaving Figure 8, it should be noted that it is so constructed as to suggest that LH stimulates only that part of the adrenal cortex which has to do with the production of 17-ketosteroids whereas the corticotrophic hormone stimulates that part which does not produce 17-ketosteroids. There is really no evidence one way or the other on this point, but in a black and white diagram it is very difficult to hedge. This point is further discussed in a previous paper.¹

It is now necessary to discuss some evidence which suggests that the above scheme may have to be modified. Until recently it has been assumed that LH plays a part in three phenomena: 1, the pre-ovulatory spurt of growth of the ripening follicle; 2, ovulation; and 3, progesterone formation by the corpus luteum. Astwood⁴ has performed some very convincing experiments suggesting that the actual production of progesterone by the corpus luteum is not mediated through LH but through the "luteo-trophic" hormone. It would appear, therefore, that many of the functions that have

been attributed above to LH may really be mediated through luteotrophin. Thus it may be luteotrophin and not LH which is stimulated by estrin. Such a thesis is supported by the fact that estrin therapy in rodents does not lead to corpora lutea formation but to increased size of corpora lutea and increased production of progesterone.^{28,42} Furthermore, it may be luteotrophin which stimulates the adrenal cortex and not LH; this suggestion gains weight from the fact that preparations containing adrenal cortical hormone also contain luteotrophin. The above explanation would take care of the disturbing fact that crystalline LH in hypophysectomized animals apparently has no effect on the adrenal cortex.^{5,18} There is some evidence, moreover, that estrin causes hyperplasia of the adrenal cortex only in the presence of a functioning corpus luteum;³⁹ it may be of some interest, therefore, that the only one of our patients who has had a definite rise in the 17-ketosteroid excretion under therapy is the one who received both estrin and progesterone (see Case 5). Finally if it turns out that neither LH nor luteotrophin stimulate the adrenal cortex then one will probably have to modify the scheme by having estrin stimulate the corticotrophic hormone directly or one of the corticotrophic hormones if there are two.

Figures 9 *A*, 9 *B*, and 9 *C* are constructed similarly to Figures 8 *A*, 8 *B*, and 8 *C*, to show the hormonal relationships in pituitary dwarfism (Fig. 9 *B*) as opposed to the normal (Fig. 9 *A*) and the effect of estrin therapy in this condition (Fig. 9 *C*). The illustrations speak for themselves. It should be noted that because of complete lack of pituitary function estrin therapy has no effect on the adrenal cortex, and, hence, no effect on axillary hair.

Classification of Congenital Ovarian Insufficiencies. At the expense of slight repetition the authors would like to enumerate four distinct clinical entities leading to "primary amenorrhea," namely: *a*, the syndrome under discussion; *b*, menopause occurring shortly before the menarche; *c*, panhypopituitarism; and, *d*, a selective underfunction of one or more gonadotropic hormones with secondary ovarian atrophy.

The first three of these conditions and their differentiation from one another require no further discussion. Needless to say, "*b*" is not a congenital ovarian deficiency but rather an acquired one.

The authors have studied 2 cases characterized by complete absence of ovarian function, primary amenorrhea, absence of short stature, absence of persistently high excretions of FSH, 17-ketosteroid excretions which are probably slightly low, small amounts of axillary and pubic hair, responsiveness of axillary and pubic hair to estrin therapy, and moderately delayed bone ages. The authors do not feel too dogmatic about this syndrome but are now in the process of studying more cases. The syndrome may be the

female counterpart of what has been called "eunuchoidism-with-negative-FSH" in males.¹⁵ In any case, the one thing the authors feel quite certain about is that the condition is not primarily ovarian but secondary to some pituitary disturbance but not to a panhypopituitarism. An acquired amenorrhea, apparently due to absence of follicle-stimulating-hormone, is not uncommon; it was discussed by Albright and Halsted.²

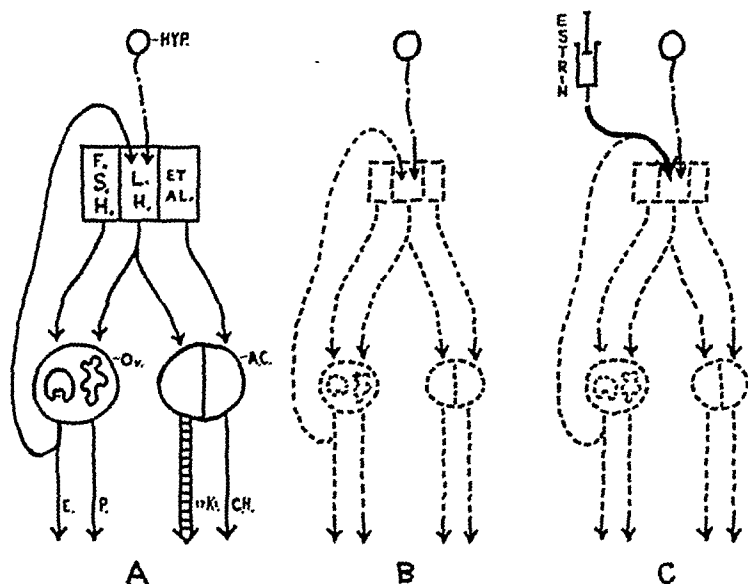


FIG. 9.—Hypothetical and schematic diagrams indicating possible interrelationships between various hormones in (A) normal status, (B) panhypopituitarism, and (C) panhypopituitarism under estrin therapy. For explanation see Figure 8; for discussion see text. Note that estrin therapy has no effect on the adrenal cortex because of absence of pituitary function.

Summary and Conclusions. 1. Eleven cases of a syndrome probably due to, and at least associated with, life-long ovarian insufficiency have been described.

2. This syndrome is characterized by infantile sexual organs, complete lack of breast development, small to moderate amounts of axillary and pubic hair in spite of complete absence of other so-called "secondary sex characteristics," short stature, the frequency of congenital anomalies especially webbing of the neck and coarctation of the aorta, late union of the epiphyses often accompanied by epiphysitis, osteoporosis, precocious senility, an excess of follicle-stimulating-hormone in the urine and a decrease but not an absence of the excretion of the 17-ketosteroids in the urine.

3. This condition is to be differentiated from pituitary dwarfism (panhypopituitarism) by the following criteria: A, The individuals

are short rather than dwarfs. *B*, The bone ages are only slightly retarded rather than markedly so. *C*, These patients have a reduced amount of axillary and pubic hair rather than none at all. *D*, Estrin therapy in these individuals leads to marked increase in axillary and pubic hair whereas it has no such effect in panhypopituitarism. *E*, These patients are quite strong and well nourished rather than weak and undernourished. *F*, The follicle-stimulating-hormone in the urine is increased above the normal rather than absent. *G*, The 17-ketosteroids in the urine are decreased but not minimal. *H*, In an insulin tolerance test these patients exhibit normal hypoglycemia responsiveness as opposed to hypoglycemia unresponsiveness.⁴⁸ These patients can have diabetes mellitus as a complication (see Case 12), whereas from the work of Houssay this complication is incompatible with panhypopituitarism.⁴⁶ *I*, These patients are prone to have other congenital anomalies.

4. The syndrome is differentiated from three other conditions causing life-long or primary amenorrhea; these are panhypopituitarism (pituitary, ateliotic, Lorain-Levi, or Paltauf dwarfs), "premenarchal menopause præcox," and a selective deficiency of the gonadotropic hormones of the anterior pituitary.

5. A discussion is included as to which hormones in females directly cause axillary and pubic hair growth; evidence is cited suggesting that this function in females depends on an adrenal cortical hormone.

6. Five hypotheses are discussed as possible causes for the diminished rate of growth in this syndrome; the authors rather believe it results from decreased adrenal cortical function which in turn results from decreased pituitary-stimulation-of-the-adrenal-cortex which in turn results from decreased estrin production.

7. Evidence is presented to suggest that Turner's syndrome—congenital webbing of the neck, sexual and somatic infantilism, and cubitus valgus—is a subform of this syndrome.

8. Emphasis is placed on a marked tendency to precocious senility in this syndrome; an analogy is drawn between the atrophied tissues after normal menopause and the atrophy exhibited by these patients at a very much younger age.

9. Replacement therapy with estrin leads to a marked increase in general well-being, causes development of the breasts and increase in axillary and pubic hair, and probably leads to an increase in the rate of growth in those subjects whose epiphyses are still ununited.

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"EPINEPHRINE SHOCK" AS A MANIFESTATION OF A PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

REPORT OF A CASE WITH SUCCESSFUL REMOVAL OF THE TUMOR

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ALTHOUGH it is well known that the administration of large doses of epinephrine intravenously to the experimental animal will result in profound circulatory failure,^{1,7,9} the development of shock-like symptoms in cases of pheochromocytoma in which there is presumably an excessive secretion of epinephrine or an epinephrine-like substance² has been noted only occasionally, and there has been little comment concerning its significance. Oberling *et al.*¹⁴ describe the case of a 28-year-old female with a pheochromocytoma who had rapid fluctuations in blood pressure from 170/125 to 220/155 and who died in shock a few hours after delivery. Evan's case,⁸ a 12-year-old girl, had 2 severe paroxysms terminally in which the blood pressure rose to 285/230 mm. and which were followed by marked tachycardia and circulatory collapse with a systolic pressure of 30 mm. The demonstration of a pressor substance in the blood closely resembling epinephrine in a case of pheochromocytoma² and the successful assays of the tumors for epinephrine strongly suggest that these shock-like states might be analogous to those produced in animals by the continuous intravenous infusion of epinephrine.⁹ In only rare cases, however, have the paroxysms been of sufficient duration in humans to make possible careful observations of the effects of prolonged "epinephrine" discharge in the human.

The present case is an unusually severe instance of this syndrome in which the attacks were induced by the most simple physiologic stimuli for epinephrine discharge and in which the attacks lasted as long as 36 hours, often terminating with a clinical picture suggestive of so-called "epinephrine shock." Because of the alarming character and frequency of the attacks, the localization of the tumor and its successful removal presented unusual difficulties.

CASE HISTORY. The patient, a 23-year-old Puerto Rican girl, had enjoyed good health until 2½ years ago when she began to have episodes

of severe frontal and occipital headaches, accompanied by dizziness, weakness, epigastric, back and neck pain. Later these became more frequent and associated with a choking sensation, dyspnea, orthopnea, palpitation, and blanching of the extremities and face, and sweating. These attacks lasted for about 15 minutes to a few hours, and were followed by a day of weakness, dizziness and mild headache. She had a severe attack 1½ years ago, associated with marked dyspnea, orthopnea, and, apparently, collapse.

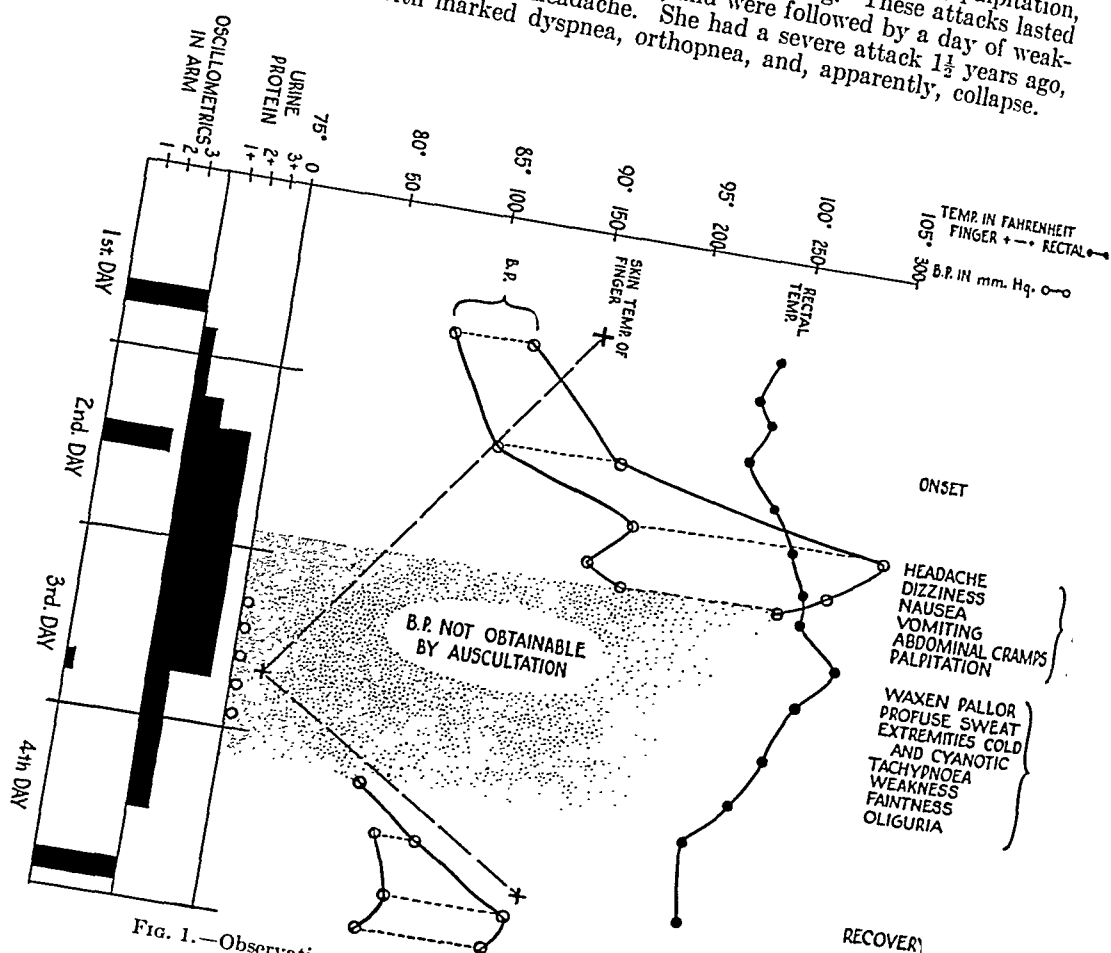


FIG. 1.—Observations during a typical paroxysm with circulatory collapse.

In a severe attack 11 months before admission, she was observed for 5 months at another hospital, during which period a number of typical attacks occurred. Because her blood pressure rose to high levels during attacks, a pheochromocytoma was suspected. During the first attempt at exploration of the left adrenal area, the induction of anesthesia precipitated a severe attack and a phlebotomy was performed because of the development of pulmonary edema. Subsequent exploration failed to reveal a tumor on the left side. Postoperatively she continued to have frequent mild attacks, although she was free of severe attacks for about 7 months. Ten days before admission a number of severe attacks occurred in rapid succession.

Physical examination revealed a frail, but fairly well-nourished girl with moderate pallor. The fundi showed slight narrowing of the arteries and somewhat hyperemic disks with indistinct margins. The heart was not enlarged. The peripheral arteries were slightly thickened. The abdomen was soft; no masses were palpable. The left biceps reflex was more active than the right; the right ankle- and knee-jerks were greater than those on the left. A left Hoffmann reflex was present. The blood count was normal. The urine showed a faint trace of albumin. The fasting blood sugar was 90 mg. per 100 cc. and urea nitrogen 14 mg. per 100 cc. Roentgenograms of the abdomen and chest showed no abnormalities. An intravenous pycelogram revealed the kidneys to be normal in size and position.

Description of a Typical Attack with Shock Syndrome. (Fig. 1.) During her stay in the hospital, the patient had frequent attacks, most of which were spontaneous and a few induced. The attacks varied in severity from lesser ones lasting an hour or more, to the most severe ones lasting over 36 hours. Between attacks her blood pressure was usually moderately elevated, ranging from 140 to 160 mm. Hg systolic and 90 to 110 mm. diastolic, but occasionally was entirely normal.

A sudden onset of palpitation, pounding headache, blanching of the face and extremities, abdominal cramps, nausea and repeated vomiting, was followed by marked diaphoresis. Blood pressure readings taken shortly after the onset showed extreme elevation, frequently over 310 mm. Hg systolic and 180 mm. diastolic. When the attack continued beyond 8 to 12 hours, during which period the patient continued to complain bitterly of pounding headache, palpitation, abdominal pain and vomiting, an interesting sequence of events ensued. The major peripheral vessels began to show evidences of progressive constriction, the pulses becoming of very small amplitude until entirely obliterated both to palpation and oscillographic determination (Table 1). At times constriction of the arteries was

TABLE 1.—OSCILLOMETRIC READINGS DURING AND BETWEEN PAROXYSMS

	Interval	Paroxysm
Right ankle	1 0	0
Right calf	1 5	0
Right thigh	2 5	less than 0 5
Left ankle	1 5	0
Left calf	3 0	0
Left thigh	3 0	less than 0.5
Right wrist	0 5	0
Right forearm	1 5	0
Right arm	4 0	less than 0 5
Left wrist	1 5	0
Left forearm	3 5	0
Left arm	3 0	less than 0.5

so great that even the pulsations of the carotid arteries were barely palpable and the pulse rate could only be obtained at the precordium. Because of the absence of audible or palpable pulsations, it became impossible to determine the blood pressure by means of the sphygmomanometer. The extremities, including the nose and ears, became extremely cold, pale, and cyanotic. The temperature of the skin, determined by the Dermatherm, showed a fall of as much as 7.6° C. in the extremities but little change over the trunk, while the rectal temperature rose to as high as 40° C. (104° F.). This gradient in skin temperature was a striking finding, repeatedly confirmed (Table 2, Fig. 1). Profuse diaphoresis over the trunk and face was always present at this time and there was usually a tachycardia, reaching

130 per minute. The neck veins sometimes appeared distended, and the patient often complained of dyspnea. The venous pressure in the ante-cubital vein, however, was found to be normal during the early part of one attack, and during a later stage collapse and constriction of the veins of the extremities was so great that venipuncture became impossible.

TABLE 2.—SKIN AND RECTAL TEMPERATURES IN DEGREES CENTIGRADE DURING AND BETWEEN PAROXYSMS

	Interval	Paroxysm
Right forefinger	32.3	24.7
Left forefinger	30.8	26.1
Right forearm	32.8	29.9
Left forearm	31.8	29.6
Right arm	32.8	30.4
Left arm	31.5	29.3
Right great toe	31.3	25.4
Left great toe	31.3	25.2
Right calf	30.8	28.4
Left calf	31.3	28.6
Right thigh	31.8	31.9
Left thigh	31.3	30.2
Abdominal wall	33.3	33.2
Sternum	33.3	31.4
Nose	31.8	24.4
Rectum	37.0	40.0

During the height of an attack the fundi showed definite changes, which were described by Dr. Lambert as follows: "In the supine position, with a blood pressure of 270/150, the arteries are somewhat thinner than normal with a bright irregular reflex and are quite irregular in calibre. They indent the veins somewhat and there is a general slight propulsive pulsation. The veins are also irregular in calibre, and are somewhat dilated. Examination after standing (blood pressure 305/170) showed what seemed to be a more general narrowing of the arteries, but no definite transitory or motile spasms could be detected."

Urinalyses during an attack regularly showed an increase in albumin to 3+, and the appearance of red cells, white cells and casts. Slight glycosuria was noted once. The blood sugar was not found to be elevated on the one occasion it was possible to do a venipuncture. Electrocardiograms during an attack showed a sinus tachycardia, high QRS, depressed R-T 1, 2 and 3 segments, and inverted T-1.

Eventually, after 24 to 36 hours, the patient showed evidences of peripheral vascular collapse, with apparent blood pressure readings obtained as low as 76/60 mm., hemoconcentration (as demonstrated by a hematocrit reading of 53%), tachycardia and torpor, while the evidences of diminished blood flow through the extremities persisted. The state of circulatory collapse would last several hours and then gradually the peripheral pulses would become fuller and slower, the extremities warm, the blood pressure would return to normal, the hematocrit would fall to its normal value of 38%, and the systemic temperature would fall, until the whole cycle was repeated with the next severe paroxysm.

Induction of the Attacks. The means to induce the attacks afforded interesting support for Cannon's concept of the emergency function of the sympathico-adrenal system.⁵ The usual stimuli for sympathetic discharge were found to produce attacks readily. Spontaneous attacks occurred during fear, anger, excitement, sexual intercourse, before meals when the blood sugar was probably falling, and during the induction of anesthesia when asphyxia probably was a factor.

Similarly, attacks were induced by analogous procedures. A change from the prone to the sitting position resulted in a rise in blood pressure from 150/110 mm. to 175/125 mm. Standing then led to a prompt fall to 155/110 mm. and then a rapid rise to 305/170 mm. in 15 minutes, with a pulse rate of 80. Massage of the carotid sinus during this maximum rise caused a transient slowing of the pulse and a prompt fall in pressure to 160/115 which, however, immediately rose on discontinuing the stimulation, demonstrating the reflex pathways to be intact and at least potentially active. On reclining, the blood pressure returned to normal only after several hours (Fig. 2). This response to posture was regarded as an excessive exaggeration of the normal postural blood pressure reaction and correlated clinically with the patient's history of attacks upon arising in the morning.

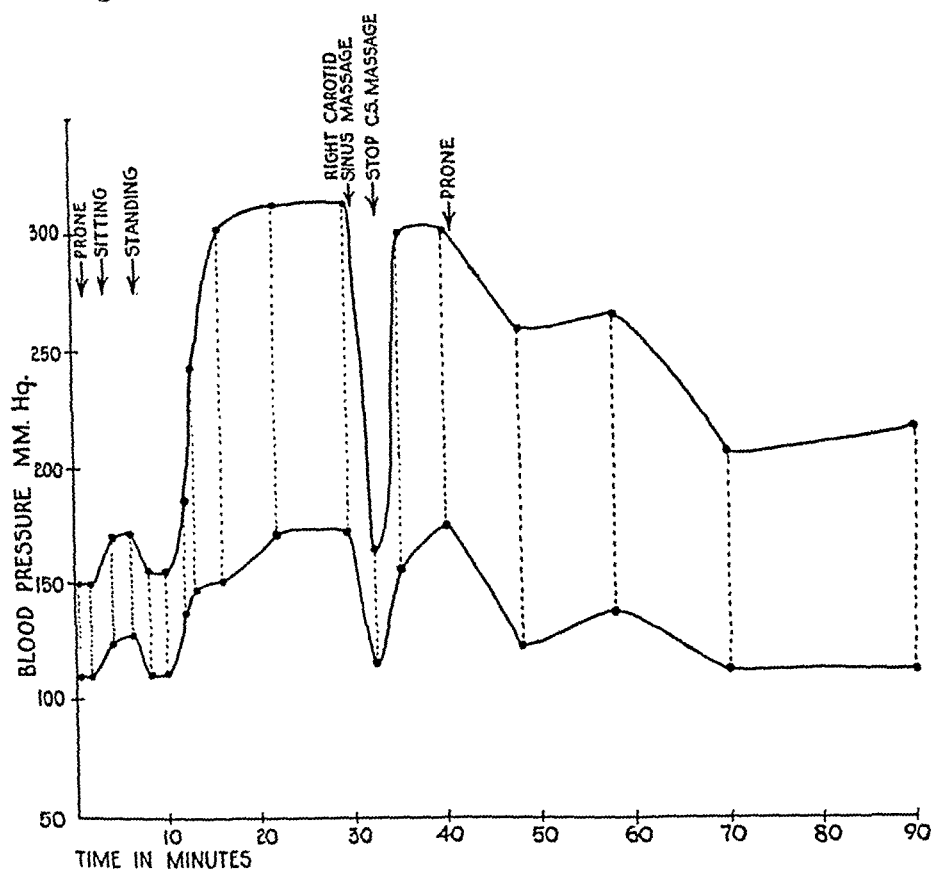


FIG. 2.—The effect of change in posture in a case of pheochromocytoma of the adrenal. Note the effect of carotid sinus stimulation.

To demonstrate that the postural reaction was not an emotional one, the patient was given 5 gr. of sodium amytal intravenously until she was asleep. During the administration of the drug the blood pressure fell from 120/90 to 94/40. The patient was then supported in the erect position and the blood pressure rose promptly to 270/160 (Fig. 3).

On another occasion, hyperventilation for 3 minutes caused a rise in pressure from 170/110 to 305/160, the pressure not yet returning to its initial value at the end of 1 hour. In this instance, mechanical massage of the tumor probably played a rôle, since at operation the tumor was found to be adherent to the diaphragm.

Cold and pain, induced by immersion of the hand in ice water for 2 minutes, caused a rise in pressure from 135/98 to 200/135 in 3 minutes, which was maintained for over an hour (Fig. 4).

Attempts to induce paroxysms by massage of the abdomen were uniformly unsuccessful. Studies with insulin, adrenalin, histamine and other drugs were not carried out because of the severity of the paroxysms. A dextrose tolerance test had to be omitted for the same reason.

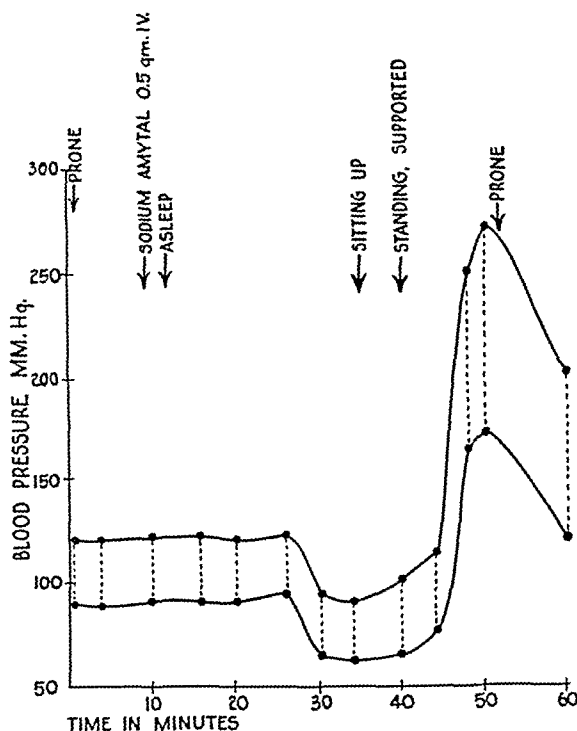


FIG. 3.—The effect of sodium amytal on the postural blood pressure response; 5 gr. of sodium amytal was administered intravenously until the patient was unconscious. The response on supporting the patient in the upright position demonstrates that the blood pressure rise on standing was not due to an emotional reaction.

Postural Blood Pressure Studies (Table 3). These were determined by the method of Gaertner on the brachial artery and the digital arteries of the middle finger of the left hand, using the Gaertner method for digital pressures. During an attack, the brachial-digital systolic difference was between 100 and 120 mm. Hg, as compared to 50 mm. after the removal of the tumor, which is within normal limits. This high differential is characteristic of the hypertension produced by epinephrine.

TABLE 3.—BRACHIAL AND DIGITAL BLOOD PRESSURES (METHOD OF GAERTNER)

	During a paroxysm	After removal of tumor
Brachial systolic pressure (mm. Hg)	220	118
	260	110
	280	110
Digital systolic pressure (mm. Hg)	130	68
	154	60
	150	54
Brachial-digital systolic blood pressure difference	90	50
	106	50
	130	56

Treatment of the Paroxysms. All measures employed to terminate attacks were without avail. Ergotamine tartrate, which is an antagonist to epinephrine was completely ineffectual in a dose of 1 mg. intravenously. Sodium amytal and other rapidly acting barbiturates gave only slight symptomatic relief, but did not appear to shorten the attacks or lower the blood pressure, except transiently. It was felt that the use of parasympathetic drugs was contraindicated because of the sympathetic rebound likely to occur after their administration. The use of plasma during the shock-like states was considered, but did not prove possible because of the extreme collapse of the peripheral veins.

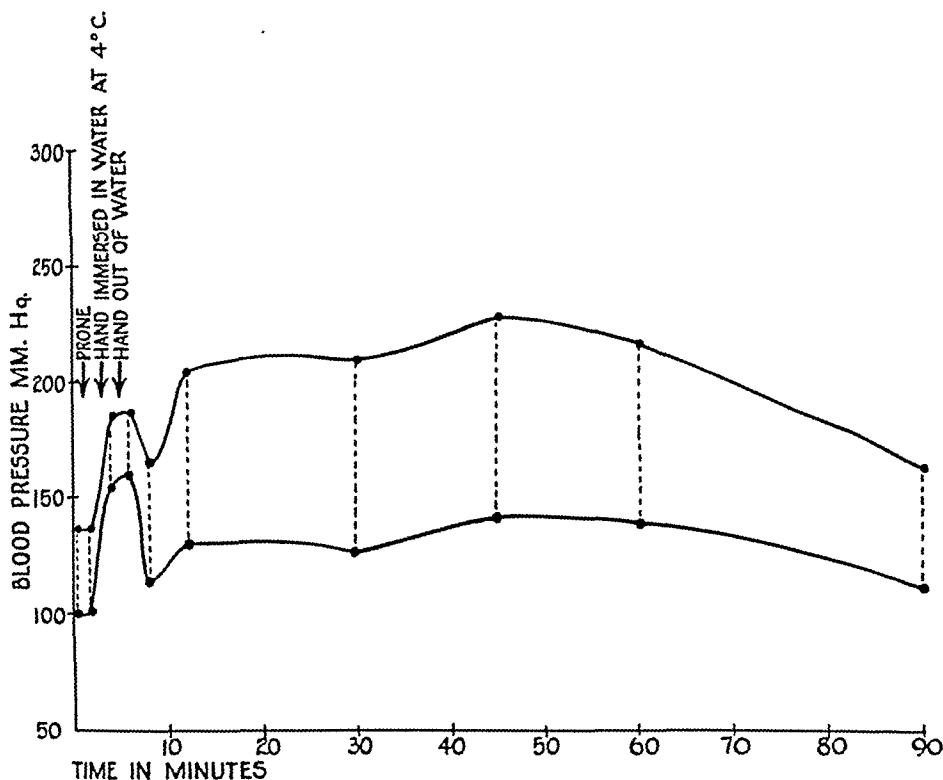


FIG. 4.—Cold pressor test. The hand was immersed in ice water at 4° C. for 2 minutes. Note the sustained rise in blood pressure.

Roentgenologic Demonstration of the Tumor (Fig. 5). Perirenal insufflation¹⁵ was performed by the instillation of 550 cc. of oxygen into the right perirenal space. There was no untoward reaction. Roentgen ray examination revealed a suggestion of a small mass in the right adrenal area, the lower portion of which was flattened and caused a flattening of the upper pole of the kidney.

Preoperative Preparation. Because of the dangers of emotional excitement, preparations were made to "steal" the adrenal as is usually done with the thyroid in cases of Graves' disease. Avertin was given as the basal anesthetic. To avoid the inevitable shock attendant upon the removal of an adrenal tumor, the patient was given desoxycorticosterone acetate (synthetic adrenal cortical steroid) intramuscularly, and glucose and saline intravenously preoperatively, adrenal cortical extract intravenously during the operation, and epinephrine hypodermically and intravenously and epinephrine-in-oil intramuscularly during and after the operation. This régime, which has been previously outlined by Biskind *et al.*⁴ was designed

to prevent the effects of the sudden withdrawal of epinephrine from the blood, which is the cause of the immediate fall in blood pressure on tying off the tumor, as well as the delayed shock which is probably due to temporary adrenal cortical insufficiency. Anoxia at the operation was minimized by the use of cyclopropane as the anesthetic.

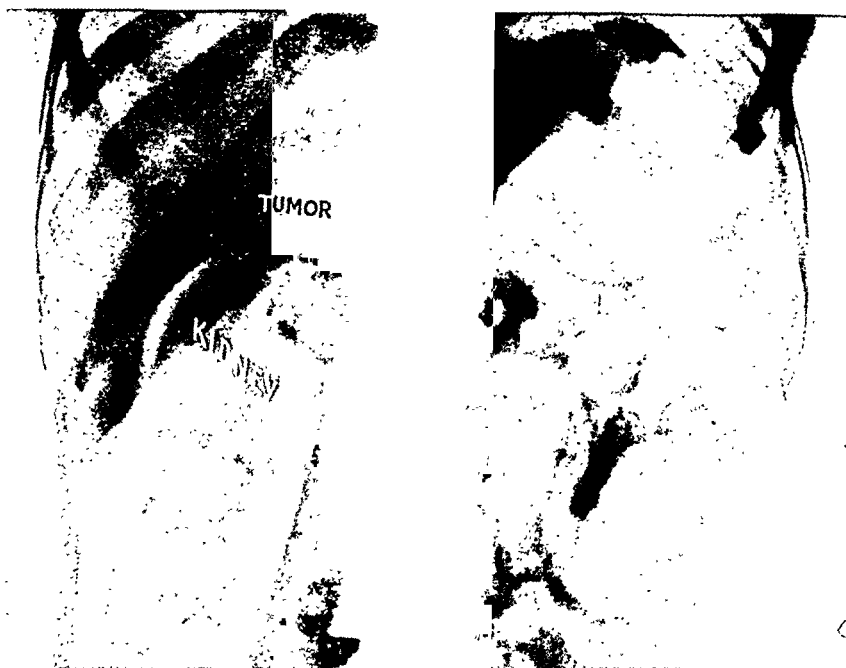


FIG. 5.—Perirenal insuflation showing the outline of the kidney and the adrenal tumor. The upper surface of the tumor was not delineated because the tumor was found to be adherent to the diaphragm. Note the flattening of the upper pole of the kidney.

Operation. Through a right lumbar incision the renal area was exposed, the kidney was mobilized and retracted downwards. A tumor the size of a large plum was found in the adrenal area. It was round, semi-soft, attached to the upper pole of the kidney and adherent to the diaphragm. At the onset of the operation, the systolic blood pressure was 120 mm. As soon as the tumor was palpated, the blood pressure rose to 220 mm. Hg, at which level the pressure was maintained almost constantly until the last vessel to the adrenal gland was ligated. At this point the blood pressure dropped precipitously to 110 mm. and then further to 70 mm. The tumor was easily removed.

LEGENDS FOR FIGS. 6, 7 AND 8

FIG. 6.—Gross appearance of the adrenal tumor. Scale in centimeters.

FIG. 7.—The tumor in section. Note the very thin section of adrenal cortex. The rest of the specimen represents the medullary tumor.

FIG. 8.—Microscopic section of the pheochromocytoma.

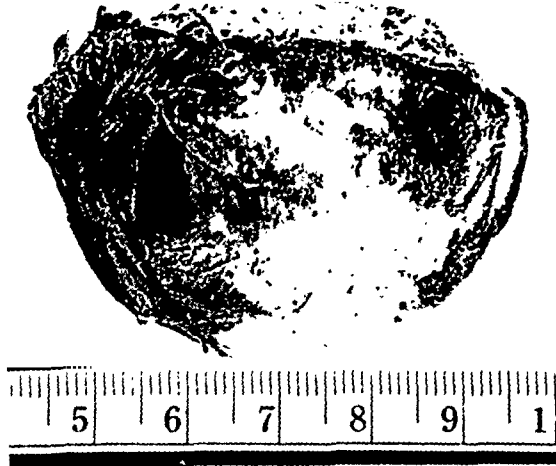


Fig. 6



Fig. 7

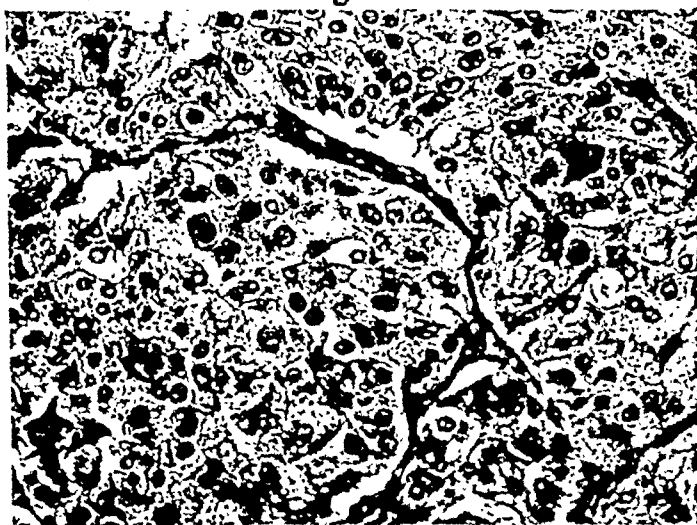


Fig. 8

(For legends see opposite page)

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During the first 12 hours postoperatively, the blood pressure ranged between 70/50 and 90/65, but the patient's general condition remained relatively good. Thereafter, the blood pressure was maintained at about 100 mm. Hg systolic and her course was uneventful.

Pathology and Bio-assay (Figs. 6, 7, 8). The tumor was found to consist of a greatly enlarged adrenal gland, weighing 31 gm. and measuring 5.5 by 3.5 cm. On section the enlargement of the gland was found to be due to the presence of a tumor occupying the central portion of the gland and uniformly expanding it. The cortex was intact and was visible as a narrow golden yellow zone spread over the surface of the tumor. The central tumor was mottled grayish brown, soft and cellular, and when immersed in dichromate solution assumed a striking dark brown appearance. Microscopically it had the characteristic structure of a pheochromocytoma (Fig. 8).

Bio-assay of the tumor was performed by Dr. M. B. Bender, who found that each gram of tumor caused a reaction in the denervated cat's iris, a retraction of the nictitating membrane, and a blanching of the sympathectomized ear equivalent to that caused by 8 mg. of epinephrine. It also caused a rise in blood pressure in the cat.

Postoperative Studies. Postoperatively the patient became entirely free of spontaneous attacks. Hyperventilation and immersion of the hand in ice water caused no significant rise in blood pressure. Postural studies revealed a mild degree of postural hypotension 1 month after operation, but this disappeared later. Oscillometric readings and skin temperature readings became entirely normal. Subcutaneous injection of 0.007 mg. of epinephrine per kg. of body weight caused no significant rise in blood pressure. The electrocardiogram returned to normal. The urine showed only a very faint trace of albumin. A dextrose tolerance test revealed a fasting value of 65 mg., a rise to 125 mg. in 1 hour and a rapid fall to 45 mg. with hypoglycemic symptoms at 4 hours. There was no evidence of adrenal cortical insufficiency either by electrolyte studies or from the subsequent course. On examination 3 months after the operation, the patient had gained 20 pounds and was entirely asymptomatic. There was no postural hypotension at this time.

Comment. This patient, who had symptoms of hyperepinephrinemia for at least $2\frac{1}{2}$ years, had attacks of such unusual severity that she presented an excellent opportunity to study the effects of prolonged epinephrine discharge in the human. A review of the literature reveals few instances in which the paroxysms were of such long duration; and those which were terminated fatally. Pincoffs¹⁶ reported a case in which the attacks lasted up to 10 hours. In Belt and Powell's case³ spontaneous attacks lasted up to 6 to 7 hours, and the terminal paroxysm, which had many features similar to the case here described, lasted 48 hours and was characterized by marked hypertension, which gradually declined, tachycardia, persistent vomiting, hyperpyrexia up to 107° F., and finally death after a period in which the blood pressure fell and the pulses became barely perceptible. In most of the reported cases attacks lasted from only a few minutes to a few hours.

Hyperpyrexia, particularly during the terminal attack, is another manifestation which has been noted several times but has received

little comment. In one of the earliest cases to be recognized,¹⁰ the patient had several paroxysms a day lasting from 1 to 4 hours with a blood pressure rise to 260/180 and fluctuations in temperature from 39.5° to 40° C. Belt and Powell's case had a temperature of 107° F. terminally and De Wesselow⁶ reported that temperature rose to 105° F. preterminally, although he does not describe the clinical state at this time. In our case, every attack which lasted more than a few hours was associated with a rise in rectal temperature to 102° to 104° F. and a simultaneous fall in skin temperatures and oscillometric readings in the extremities. This rise in internal body temperature may be considered as due both to the increased heat output caused by epinephrine, which Cannon has found to amount to 50 calories per mg. of epinephrine,⁵ and to failure to dissipate heat by normal channels at an equivalent rate because of the marked peripheral vasoconstriction and decrease in peripheral blood flow.

The occurrence of marked vasoconstriction in the extremities with subjective and objective coldness, has been noted in almost all cases and is a classical feature. Beer, King, and Prinzmetal² reported decreased skin temperatures and oscillometric readings during an attack and described unusual vasomotor changes in the extremities. MacKenzie and McEachern¹² mention inability to palpate the pulse at the wrist during an attack. Mayo¹¹ noted obliteration of the capillaries of the nail beds during attacks. In no reported case, however, did the vasoconstriction assume the remarkable degree it did in our case, in which all peripheral pulses became impalpable and remained so for many hours. The marked fall in skin temperatures in the extremities was another evidence of the striking decrease in blood flow during the paroxysm. These changes were associated with a subjective feeling of coldness and paresthesiae and objectively by marked pallor and mottled cyanosis. The changes in the small vessels were also reflected in the fundus which presented a picture of constriction and propulsive pulsation in the arteries during the attacks.

The chain of events during a typical paroxysm terminating in a state of peripheral vascular collapse bears a striking resemblance to the phenomena which occur in animals receiving large doses of epinephrine intravenously. That massive doses of epinephrine can produce a fatal type of circulatory collapse is well known.^{1,7,9} In a recent study, Freeman, Freedman and Miller⁹ found that a continuous intravenous infusion of epinephrine into dogs at the rate of 0.0034 to 0.0164 mg./kg./min. for a period of 1 to 1½ hours resulted in a decrease in plasma volume and shock. When the epinephrine injection was started, the blood pressure rose rapidly to 250 to 320 mm. Hg, and the rate of blood flow through the paw decreased

to less than 1 cc. per 100 cc. of paw volume. The blood pressure then declined slowly, but was maintained throughout the period of injection at a level higher than normal, falling sharply when the epinephrine infusion was stopped. Usually within 10 minutes of the beginning of the infusion the mucous membranes of the mouth were seen to become pale and then cyanotic. At the end of 50 to 60 minutes the signs of clinical shock were marked. The extremities and ears were cold and had a doughy feel. The pulse was thready and the flow of blood in the ear veins slow and the blood dark. The rectal temperature rose rapidly. The hemoglobin rose and the plasma volume decreased by about 30%. The authors interpret the shock as the result of the severe reduction in blood flow resulting in anoxia in the peripheral capillaries, with consequent increased capillary permeability and loss of fluid and protein into the surrounding tissues. Due to progressive loss of plasma volume the vasoconstriction is unable to maintain the blood pressure which declines slowly. "The combination of loss of circulating fluids and peripheral vasoconstriction produce the clinical manifestations of shock. When the adrenalin is stopped and the blood-vessels allowed to relax, reflex vasoconstriction in response to the lowered pressure is insufficient to maintain adequate circulation to vital centers because of the fall in circulating blood volume." This mechanism also undoubtedly comes into play in the shock which almost invariably follows the surgical removal of these tumors. The close resemblance between this syndrome produced experimentally in dogs and the clinical picture presented by the patient cannot be overemphasized.

In the management of these cases the importance of pre- and postoperative care must be emphasized again. Before operation every care should be taken to avoid the excitation of an attack, particularly by the emotional stimuli attendant upon the preparations for operation. Biskind *et al.*⁴ have recently discussed the rationale and value of the use of both adrenal cortical hormones and epinephrine in the management of these cases. On removing such a tumor not only is there a sudden release from what had been probably a high level of circulating epinephrine, but also a decrease in cortical tissue which may produce a temporary adrenal cortical insufficiency. Furthermore, Parkins *et al.*¹⁵ have demonstrated that the circulatory collapse of epinephrine shock may be largely alleviated by the administration of adrenal cortical hormone. Our patient was primed with desoxycorticosterone and salt preoperatively and received cortin and epinephrine during and after the operation. Epinephrine in oil was used because of its prolonged action.

The transient development of postural hypotension after the removal of the tumor is of interest as a possible manifestation of a

temporary decrease in the capacity for peripheral vasoconstriction on assuming the erect posture. This reaction is essential to the maintenance of normal blood pressure on changing posture. Although this may have been merely the aftermath of the operation and the resultant enforced bed-rest an additional factor may have been a defective ability of the vessels to constrict in response to normal vasoconstricting stimuli after having been subjected so long to the intense vasoconstricting effect of epinephrine.

Summary. 1. A pheochromocytoma in a 23-year-old woman is reported. Symptoms had been present for $2\frac{1}{2}$ years and were of increasing severity.

2. Spontaneous attacks of unusual length and severity occurred, often ending in a state of peripheral vascular collapse. A comparison between these attacks and the phenomenon of "epinephrine shock" in dogs is made and the physiologic significance of these discussed.

3. Attacks were precipitated by the most simple mechanisms for eliciting sympathetic discharges. The significance of these reactions is discussed.

4. The tumor was localized by perirenal insufflation and successfully removed. The importance of preoperative and post-operative management is emphasized.

5. Postoperatively the patient developed a transient postural hypotension and low sugar tolerance curve with hypoglycemia which are interpreted in light of the balance between the sympathico-adrenal and vago-insulin systems.

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CLINICAL EXPERIENCE WITH RADIO-PHOSPHORUS IN THE TREATMENT OF CERTAIN BLOOD DYSCRASIAS*†

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THROUGH the courtesy of Dr. John H. Lawrence, of the Berkeley Cyclotron Laboratory of the University of California, we have, since March, 1941, been supplied with sufficient radio-phosphorus to treat a group which now comprises 38 patients classified as follows: Polycythemia vera, 8; chronic myelogenous leukemia, 5; chronic lymphatic leukemia, 4; acute leukemia, 4; Hodgkin's disease, 5; lymphosarcoma, 6; multiple myeloma, 1; reticuloendotheliosis, 1; reticulum cell sarcoma, 1; and metastatic carcinoma, 3.

The achievements of Dr. E. O. Lawrence and his co-workers¹ in the production of radio-active substances are well known. Suffice it to say here that radio-phosphorus, having an atomic weight of 32 and therefore designated as P^{32} , is produced by the bombardment of ordinary red phosphorus, whose atomic weight is 31, by very rapidly moving deuterons generated in the Cyclotron. The resulting material, converted into an aqueous solution of dibasic sodium phosphate, retains all the properties of ordinary phosphate, with the addition of radioactivity. An amount of material which emits 3.7×10^7 beta-particles of radio-activity per second is said to contain 1 millicurie of beta-radiation. Because of many complex factors it is difficult and misleading to attempt to equate the millicurie with the "r" unit of familiar usage. Roughly, however, it may be said that a 50 kg. man who absorbs and distributes equally throughout the tissues a single millicurie dose of radio-phosphorus will have the equivalent of 0.7 "r" whole body irradiation in 24 hours. As P^{32} , however, is handled by the animal organism like ordinary P^{31} , the distribution is never equal. It is quickly concentrated in bone-marrow, liver, spleen, bones, and so forth. Furthermore, as in other radio-active elements, there is constant breakdown and decay. P^{32} has a half-life of only 14.3 days, in contrast to radium and thorium which have half-lives of hundreds of years. Thus with P^{32} there is no danger of cumulative radiation effects. Finally, nearly 50% of any given dose is normally excreted during the first 6 days and excretion continues thereafter. Thus after 6 weeks no

* Presented April 15, 1942, before the Post-Graduate Institute of the Philadelphia County Medical Society.

† As both authors left Philadelphia on active service before this report was received, it is published with slight changes for which they are not responsible.—EDITOR.

significant amount of radiation can be found in any tissue following a single administration of P^{32} .

Dosage and Methods of Administration. The material, in solution, may be administered orally or parenterally. Single oral doses have varied from 1 to 20 mc. Single intravenous doses have varied from 0.2 to 2 mc. Less than 3 gm. of sodium phosphate have been administered orally in each dose; less than 1 gm. when given intravenously. Oral administration is accomplished by mixing the required dose with equal parts of orange juice. The mixture is swallowed before breakfast (with all laxatives interdicted for 24 hours before and after).

Too much phosphate (*i. e.*, too great a volume of low potency P^{32}) may produce diarrhea. This is wasteful and should be avoided. The material when administered by mouth is, in our experience, pleasant to take and free from untoward reactions.

The solution used intravenously is the same as that given by mouth. It is sterilized and kept in a vaccine bottle. The first doses are usually small, 0.1 to 0.3 mc. If well tolerated, larger quantities (1 to 3 mc.) may be administered.

The frequency of administration of radio-phosphorus follows no set rule. Some individuals receive the drug once each week, others 3 or more times a week. Usually repeated small doses are preferable to the single large one. The total number of doses varies according to the hematologic and clinical status and response of the patient.

No severe immediate reactions to radio-active-phosphorus solution have been observed. One patient died within 24 hours of administration of the drug by mouth. We are reasonably certain that the drug did not cause the fatality. Two patients complained of symptoms which strongly suggested mild radiation sickness. In one, nausea developed 2 weeks after an intravenous injection. The second individual developed nausea within a few days. If these represent true radiation sickness, they must indicate a very marked sensitivity of the individuals concerned.

Polycythemia Vera. Of 8 patients with polycythemia vera 4 were markedly improved both clinically and hematologically; 1 was unimproved, 1 only slightly improved and 2 have just begun treatment. The remissions obtained have lasted as long as 6 months and may last longer. Two patients have begun to show hematologic relapse after 6 and 7 months, respectively. Improvement may begin within 2 weeks of treatment but full hematologic effect is rarely obtained until treatment for 2 or 3 months has been carried out. There have been no deaths in this group of patients.

Chronic Myelogenous Leukemia. One of the 5 patients treated with radio-active-phosphorus obtained an excellent remission which lasted several months. A second patient, now being treated seems to be responding satisfactorily. Three patients in late stages of the disease were unimproved by the drug. One of these died before

enough drug could be given, and a second has become radiation-fast due to considerable previous Roentgen therapy.

Chronic Lymphatic Leukemia. Two of the 4 patients with chronic lymphatic leukemia obtained good remissions. Here again it is too soon to tell how long the improvement will last. One of the latter has remained in excellent condition for almost a year. One very ill patient died shortly after being given the drug by mouth (coincidental death, P^{32} not responsible) and 1 patient has only recently begun to receive radio-phosphorus.

Acute Lymphatic Leukemia. None of the 4 patients with acute leukemia was benefited by radio-phosphorus.

Hodgkin's Disease. One of the 5 patients with Hodgkin's disease was considerably improved for a few months following the drug. This was a patient who was becoming Roentgen therapy-fast after 2 years of treatment. Four patients were not benefited by the drug. Of these, 3 had received previous Roentgen therapy. The fourth patient had a huge mediastinal mass that did not respond to P^{32} but did regress with sizable Roentgen exposures.

Lymphosarcoma. Two of the 6 patients with lymphosarcoma had good remissions following radio-phosphorus therapy. One of these had become Roentgen therapy-fast and has now been clinically improved for 6 months. Two patients were benefited for several months, with regression of subcutaneous masses, following which both suffered relapses. One patient, *in extremis* and anuric for days, improved and voided 7000 cc. following a single oral dose of 2.5 mc. of radio-phosphorus. The significance of this observation is uncertain, as the patient died of his disease shortly thereafter.

Multiple Myeloma. The 1 patient treated with radio-phosphorus was not benefited by the drug.

Reticuloendotheliosis. The 1 patient treated with radio-phosphorus improved remarkably. It is noteworthy that this patient had not responded satisfactorily to moderate Roentgen ray exposures.

Reticulum Cell Sarcoma. The 1 individual treated had previously received massive quantities of Roentgen rays and had become therapy-fast. He was not benefited by moderate doses of P^{32} .

Metastatic Carcinoma. Three patients, 2 with extensive gall-bladder carcinoma, and 1 with disseminated breast malignancy were not benefited by radio-phosphorus. The total amount of drug given these patients was probably not large enough to effect such radio-resistant neoplasms.

Summary and Conclusions. Administration of P^{32} has proven to be at least equal in value to older methods of radiation therapy in certain of the malignant blood dyscrasias.

In some respects it is superior: ease of administration, absence of marked radiation sickness, more concentrated effect on bone-

marrow with perhaps more prolonged remission in chronic leukemia and in polycythemia vera.

P³² has in our experience been of no value in the acute leukemias.

From the economic standpoint it is impossible to compare P³² with ordinary Roentgen ray therapy. Such comparison will have to await the end of the war when more of these great cyclotrons may be constructed and more material may become available. At present the supply is inadequate and the newly discovered metal-lurgic uses of the cyclotron and its products are threatening to eliminate its use for clinical medicine altogether for the duration of the war.

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THE INFLUENCE OF BLOOD TRANSFUSION AND INJECTIONS OF BURSA PASTORIS (SHEPHERD'S PURSE) EXTRACT ON THE CLOT RESISTANCE IN TWO HEMOPHILIACS

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In a previous communication¹ we described a new phenomenon regarding hemostasis which we called "clot resistance." Clot resistance was tested by applying a cuff pressure around the arm after bleeding had stopped from a finger-prick wound. This simple clinical procedure tests the ability of the clot, which has formed in the prick wound, to resist increases of pressure in the capillaries, arterioles and venules. We believe clot resistance is a measure of hemostasis, since one estimates both the solidity of the clot, and its ability to adhere to the skin wound.

In 55 normal subjects, 5 or more minutes following the cessation of bleeding from the prick wound a cuff pressure of 100 mm. of mercury for 3 minutes did not cause a renewal of blood flow. This was interpreted to mean that the clot which had formed inside of the prick wound was capable of withstanding cuff pressures up to 100 mm. Hg. In 2 cases of hemophilia, however, this pressure always dislodged the clot and renewed bleeding. Studies were done before and after blood transfusion and injections of *Bursa Pastoris*

* Aided in part by a grant from the Dazian Foundation for Medical Research.

extract in order to determine if such therapy would increase the clot resistance in the 2 hemophiliacs.

Methods. A constant temperature bath (37.5° C.) capable of heating 400 cc. of physiologic saline was constructed. The finger tip was cleaned with alcohol, and immersed for 2 minutes into the bath. The heated phalanx was removed temporarily while a prick wound was inflicted with an automatic lancet (blade dimensions: 0.5 x 2 x 6 mm.), after which the finger was immediately immersed into the bath. The distal area of the finger tip should be used, since injury to the periosteum or the bone is least likely. Bleeding times were accurately measured this way with a stop watch.^{1,2} Cuff pressures of 40 to 100 mm. Hg were applied at various intervals after bleeding stopped. From 60 to 80 cc. of 2.5% sodium citrate solution were used with 500 cc. blood for transfusion. Doses of 3 cc. and 5 cc. of *Bursa Pastoris* extract* were given intramuscularly or intravenously. In these studies clot resistance tests were done by applying for 3 minutes 100 mm. Hg cuff pressure 5 and 15 minutes after bleeding had stopped. The systolic blood pressure should always be above the applied cuff pressure.¹⁰

TABLE 1.—THE EFFECT OF VARIOUS CUFF PRESSURES ON THE CLOT RESISTANCE IN 2 HEMOPHILIACS

Minutes after termination of bleeding time test	Case E. N. Mm. of Hg cuff pressure			Minutes after termination of bleeding time test	Case M. C. Mm. of Hg cuff pressure				
	0	40	100		0	40	60	80	100
1-2	+			1-3					+
2-6	-			3-15	-				
6-7	+			15-30	-				
7-8	-			30-33					+
8-9	+			33-34	-				
9-10	-			34-50	-				
10-14	+			50-62			-		
14-75	-			62-72				-	
75-81			+	72-75	-				
81-84		-		75-78					+
84-86	-			78-81	-				

+ bleeding; - no bleeding.

Results. Table 1 demonstrates a decreased clot resistance and abnormal bleeding from a finger-prick wound in 2 hemophiliacs. Case E. N. (colored, 18 years) showed a renewal of blood flow four times within 14 minutes without cuff pressure. Application of 100 mm. Hg cuff pressure 75 minutes after bleeding had stopped provoked a flow of blood from the prick wound. Lowering the cuff pressure from 100 to 40 mm. Hg was followed by a cessation of the flow within 30 seconds. In case M. C. (white, 24 years), no bleeding was observed without cuff pressure following the bleeding time test. Renewal of bleeding occurred three times following cuff pressures of 100 mm. Hg. Lowering the pressure to 40 mm. Hg caused the bleeding to stop within 7 to 20 seconds. In both cases pressures of 100 mm. Hg were necessary to dislodge the clot, since pressures of 40 to 80 mm. Hg did not renew bleeding.

Even though the bleeding time was normal and arrest of hemorrhage occurred after the clot-resistance test, spontaneous bleeding took place in both cases subsequent to the bleeding tests after intervals of 1 and 3 days. Case E. N. developed bleeding from the prick wound on the second day and persisted to bleed for 2 days with hematoma formation. In case M. C., 3 days following the bleeding tests, a hematoma developed which involved the whole finger. On the 13th day the finger bled for 1 day from the prick wound. Nine months later the bleeding tests were repeated at which time 10 cc. of *Bursa Pastoris* extract were injected subcutaneously. No bleeding occurred afterwards.

Table 2 indicates that the other tests which were done in both patients were symptomatic for hemophilia, and that the blood pressure was normal.

TABLE 2.—ADDITIONAL DATA IN THE 2 HEMOPHILIA PATIENTS

Tests	Patient E. N.	Patient M. C.
Coagulation time (Howell)	40 min.	54 min.
Prothrombin time (Quick ¹²)	19 sec.	20 sec.
Bleeding time (Copley and Lulich ^{1,2})	182 sec.	168 sec.
Platelet count (Copley and Robb ³)	250,000	420,000
Syneresis (clot retraction)	Positive	Positive
Thixotropy ⁴ (reclothing phenomenon)	Positive	Positive
Blood pressure	114/75	120/80

TABLE 3.—THE INFLUENCE OF BLOOD TRANSFUSION AND BURSA PASTORIS EXTRACT ON THE CLOT RESISTANCE IN 2 HEMOPHILIACS

Patient	Date, 1942	Blood, cc.	<i>Bursa Pastoris</i> extract, cc.	Bleeding time, sec.	Coagulation time, min.	Clot resistance. Following bleeding time test cuff pressure applied after	
						5 min.	15 min.
E. N.	1-23			160	300 300	+	+
	1-23	500					
	1-24	500					
	1-24		6				
	1-25			105	7 10	—	—
E. N.	3-11			30		+	+
	3-11	500					
	3-12			205	226 286	+	+
	3-12		6				
	3-13		3				
	3-13			95	145 320	—	—
M. C.	3-14			105	30 50	+	+
	3-14	500					
	3-14			54	150 150	+	+
	3-15			80	65 135	+	+
	3-15		10				
	3-16			60	79 79	—	—
	3-16			130		—	+
	3-16						

+ bleeding; — no bleeding.

Table 3 shows results on clot resistance, bleeding time and coagulation time which were done 6 months or more after the initial findings shown in Table 1. The coagulation time in duplicate tests may vary from the same withdrawal. The shorter coagulation time was found, when the blood which entered the syringe first was mixed with tissue juice. Case E. N. was studied on 2 occasions; the first time while he suffered from a periapical abscess, and the second time when he complained of hemorrhages in the right arm. On the first occasion E. N. received two 500 cc. transfusions of citrated blood, and within the next 12 hours 6 cc. of *Bursa Pastoris* extract. No studies were done after the transfusions. However, 15 hours following the combined therapy of blood and *Bursa Pastoris* extract, the coagulation time was reduced to the normal range, and the clot resistance was increased. When this patient was studied again 6 weeks later, the clot resistance was found to be decreased. Coagulation studies were not done prior to transfusion; however, 18 hours following a 500 cc. transfusion, the coagulation time was still definitely prolonged and the clot resistance was decreased. This patient then received 9 cc. of *Bursa Pastoris* extract, and it was found that the coagulation time was not affected, but the clot resistance was increased. Case M. C. was studied when he entered the hospital complaining of hemorrhages in the right hip. Before transfusion, the coagulation time was 30 and 50 minutes and the clot resistance was decreased. Two tests were performed after the transfusion in intervals of 1 and 16 hours. In each instance the clot resistance was decreased, and the coagulation time was longer than it was before the transfusion. Ten cc. of *Bursa Pastoris* extract were injected. The bleeding time, coagulation time and clot resistance tests were repeated on the next day. The *Bursa Pastoris* extract again exerted no apparent influence on the coagulation time. However, the clot resistance in two successive tests was increased. In the second test 15 minutes after bleeding had stopped a minimal output of blood occurred. Usually the output of blood during positive tests was great in this patient.

Discussion. The results indicate that the firmness of the clot, or its ability to adhere to the wound, was abnormal in both cases of hemophilia. The clot resistance was found to be decreased on several different occasions in a period of time which lapsed over 6 months or more. The quality of the clot in hemophiliacs also explains recurrence of bleeding from the same wound which, although minor, continues to bleed until spontaneous arrest occurs, or persists until death ensues. The spontaneous recurrence of bleeding from the wound and into the finger suggests that movement of the arm or slight trauma to the finger dislodged the clot and renewed bleeding. This phenomenon was observed following the bleeding tests when nothing was given after the determinations. However, the phenomenon of spontaneous bleeding from the prick wound

never occurred when either the *Bursa Pastoris* extract alone, or combined with blood transfusion was given. Further, the effect of *Bursa Pastoris* extract upon the clot resistance in hemophiliacs is evident from our results. Whether this effect on the clot resistance is due solely to the extract of *Bursa Pastoris*, or the combined action of citrated blood and the former remains to be determined. We feel that the clot resistance test may also be of value in other hemorrhagic conditions.

In one instance, we found a normal coagulation time following the administration of blood and *Bursa Pastoris* extract. On two other occasions, however, neither the blood transfusion nor the injection of *Bursa Pastoris* extract appreciably shortened the coagulation time, whereas the clot resistance was increased. It has been shown by Johnson⁹ that transfusions of 500 cc. of citrated blood will shorten the coagulation time within 30 minutes and that this effect may persist for 68 hours. We did not find this result from citrated blood in the two instances which we studied. In case E. N. there seemed to be no appreciable decrease of coagulation time; whereas in case M. C. a prolongation occurred 2 and 16 hours following the transfusion. This indicates that a shortening of the coagulation time following transfusions of 500 cc. of citrated blood may not necessarily occur. This is also true following the injections of 9 to 10 cc. of *Bursa Pastoris* extract.

Steinberg and Brown¹⁴ who first made extracts from *Bursa Pastoris* and various other plants stated that the active hemostatic agent of the plant extracts was oxalic acid and that dicarboxylic acids when injected shorten the coagulation time. However, it will have to be established if the hemostatic action of *Bursa Pastoris* extract is due solely to dicarboxylic acids. It might well be that the hemostatic action of the plant extract is due to a phytothrombin,⁵ a plant thrombin which is known to exist in papain^{5,6} and which may be present in *Bursa Pastoris*. Previous to this study one of us (A. L. C.) searched the literature concerning *Capsella bursa-pastoris* Medic. *Cruciferae* (Shepherd's Purse, Mother's Heart) and found that it is a plant which was well known and used as a hemostatic agent locally and internally several centuries ago.^{7,11} Shepherd's Purse is one of the commonest weeds throughout North America and was introduced from Europe.¹⁵ It was consumed in this country⁸ and in China¹³ as a vegetable. Therefore it cannot be very toxic. In view of this, the present findings with *Bursa Pastoris* extract and the use of Shepherd's Purse in former times as an internal hemostatic, it is possible that this plant or its extracts when taken orally may exert a hemostatic effect.

Summary. 1. A decreased clot resistance and abnormal bleeding from the finger wound was found in 2 hemophiliacs on several occasions over a period of 6 or more months.

2. The bleeding time which was measured previous to the clot resistance test was always within normal limits.

3. Injections of extract of *Bursa Pastoris* following blood transfusion increased the clot resistance in both hemophiliacs.

4. The coagulation time was found shortened on one occasion with the combined treatment of transfused blood and injected *Bursa Pastoris* extract, however in two other trials it was not affected significantly.

5. Apparently, no direct relationship exists between the coagulation time and the clot resistance.

6. The hemostatic effect of the plant *Bursa Pastoris* is discussed.

We wish to thank Dr. R. H. Major who made the hospitalization of both patients possible, Dr. M. Allen who in the course of this study suggested that we determine the effect of the plant extract upon the coagulation time, and both patients for their coöperation.

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THE SPINAL FLUID IN TUBERCULOUS MENINGITIS

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THE spinal fluid in tuberculous meningitis is characteristically supposed to be clear, to be under increased pressure, to have a high cell count with lymphocytes predominating,⁶ to show decreased sugar and chlorides, usually to contain increased globulin as determined by Pandy's or Noguchi's test, constantly to contain tubercle bacilli and an increased amount of protein and to give a Lange curve of approximately 0003334444.

According to Levinson,³ different kinds of protein in the spinal fluid distinguish tuberculous from "suppurative" meningitis. He has advocated a chemical test to differentiate meningitis due to the

tubercle bacillus from other types of meningitis. In "suppurative" (non-tuberculous) meningitis sulphosalicylic acid gives a precipitate three times as great as mercuric chloride. In tuberculous meningitis the bichloride precipitate is supposed to exceed that of the sulphosalicylic acid.

Other authors² refer briefly to the possibility of the spinal fluid in tuberculous meningitis exhibiting predominantly neutrophilic cells. Others⁵ admit the possibility of the spinal fluid cellular increase being neutrophilic, but only in those tuberculous meningitides complicated by some other infection. Few of the textbooks (Naegeli⁸) will grant with Sahli¹¹ that the spinal fluid in unmixed tuberculous meningitis may be cloudy* and contain an excess of neutrophils.

Merritt and Fremont-Smith⁷ found no "frankly purulent" fluids in 84 patients with proved tuberculous meningitis. Most of the fluids were clear. A few had a ground-glass appearance. The neutrophil cells exceeded the mononuclears in 16 of 141 fluids. According to Purves-Stewart,¹⁰ in an acute advancing tuberculous meningitis, 30% of the cells in the spinal fluid may be neutrophils. They may be present in the spinal fluid of patients with tuberculous meningitis according to Weschsler.¹² Oppenheim⁹ found exceptions to Widal's dictum that tuberculous meningitis is characterized by the predominance of lymphocytes; purulent and cerebrospinal meningitis by neutrophils. Ford and Forsyth¹ hold tubercle bacilli are found in most spinal fluids of tuberculous meningitis.

Wilson and Bruce¹³ state that there is a pleocytosis of 200 or more cells in the acute stages of tuberculous leptomeningitis. Neutrophils may predominate at the onset. They quote Birkel's finding of 8 turbid fluids in 189 specimens. They ascribe frankly purulent fluids to a secondary or mixed infection.

Having recently encountered 2 proved instances of unmixed tuberculosis of the meninges with cloudy spinal fluid and a pleocytosis of neutrophils in both cases, I investigated the spinal fluid findings in 111 other patients with tuberculous meningitis verified by autopsy or by finding tubercle bacilli in the spinal fluid. In 17 of these tuberculous meningitis was shown in each by isolating tubercle bacilli from the spinal fluid and also by autopsy.

In 35 cases the diagnosis was made from the presence of tubercle bacilli in the spinal fluid. In 66 the diagnosis was confirmed by autopsy only, by culturing tubercle bacilli from the spinal fluid on Herrold's medium⁴ and later by autopsy. In 1 instance the tubercle bacilli were seen microscopically and cultured on Herrold's medium. In 5 cases the tubercle bacilli were seen and produced tuberculosis

* "Cloudy" is taken to be synonymous with turbid; the wire of the usual culture loop can barely be distinguished through a test tube of the fluid.
 "Purulent" fluid is taken to be so turbulent and opaque that a culture loop cannot be seen through an ordinary test tube of it. The opacity is due to leukocytes (understood to be polymorphonuclear) and serum proteins.

in guinea pigs. In 3 instances a positive guinea pig inoculation was the only proof. In 1 patient tubercle bacilli were found only on guinea pig inoculation. This patient later showed tuberculous meningitis at autopsy. In all, autopsies were obtained in 76 instances. The records of 111 patients were obtained from the Cook County Hospital and the Presbyterian Hospital of Chicago. Two patients were in the West Suburban Hospital. These hospitals are general hospitals.

Analysis of Data. All of the patients died. In age they ranged from 6 weeks to 58 years. Patients aged 10 years or less were more than three times as numerous (58% of total number) as those over 30 years (18% of total number). There were 33% more males than females.

In 12 of the patients the fluid was cloudy and contained over 312 cells. In 4 of these cloudy spinal fluids the predominating cells were neutrophils. In 4 cloudy fluids the character of the cells was not studied.

Cells in the spinal fluid varied from 30 to 3000, 210 being the average number of cells in the spinal fluid. In 14 patients there were more than 100 cells in the spinal fluid. In 12 cases one-half or more of the cells were neutrophils. In 7 patients only neutrophils were seen in the spinal fluid. The course of the patients with neutrophilic pleocytosis did not differ in duration or severity from that of patients with the more usual preponderance of lymphocytes in the spinal fluid. The patients with spinal fluid cells predominantly neutrophilic were as frequently adults as infants.

The Pandy test was reported as positive in 112 of the 113 patients.

Total protein of the spinal fluid measured 20 to 712 mg. per 100 cc. It tended to parallel the degree of pleocytosis.

Two-thirds of the patients showed leukocyte counts in the peripheral blood of less than 10,000. Of the 65 instances with a differential count, 57 showed a predominance of neutrophils in the peripheral blood. This contrasts with Merritt and Fremont-Smith's⁷ finding of a relative neutrophilia in only 16 cases of 141 studied.

In 5 of 16 patients Levinson's test gave incorrect results; denoting suppurative meningitis rather than the demonstrated tuberculous meningitis. In these cases the spinal fluid was clear to opalescent and there was no secondary infection.

Tubercle bacilli were found in 35 of the 81 patients whose spinal fluid was examined bacteriologically. Consequently in only 40% was this finding of value in bedside diagnosis.

Spinal fluid sugar was below 45 mg. per 100 cc. in the 25 patients with quantitative estimates.

The Mantoux test was negative in a boy of 13 years, a patient with tuberculous meningitis verified by autopsy.

Case Reports. CASE 1. Mrs. G., 28 years old, entered West Suburban Hospital in delirium under care of Dr. M. P. Palmer. She had vomited

and had headache for 2 days. Tuberculous lymph glands had been removed from her neck 2 months before. Roentgen rays of her chest were reported as negative.

Essential Findings. Temperature 103°, pulse 120 and respirations 30. Patient was thin but had good color. Irrational. Bilateral papilledema. No choroidal tubercles. Left eye lags on looking upward, otherwise no involvement of cranial nerves. Tuberculous laryngitis without hoarseness. Neck was stiff. Cervical lymph glands enlarged. Heart and lungs negative. Abdomen negative. Choreiform movements of right arm. Reflexes: those of the right arm less than on left, abdominal absent, right knee jerk sluggish, plantar normal. Blood leukocytes were 7200 per c.mm. Spinal fluid: cloudy, pressure 240 mm., total protein 850 mg., sugar 27 mg., 456 cells, 90% polymorphonuclear. Ross-Jones positive. Wassermann test negative; Large number of bacteria seen. Many cultures on various mediums yielded no growth. A guinea pig inoculated with the spinal fluid showed tuberculosis at autopsy.

The temperature climbed each afternoon to reach 106° on the sixth day of her illness, the day of her death.

Essential postmortem findings (Dr. E. Piette): chronic tuberculous laryngitis, recent miliary tuberculosis of both lungs, fibrous adhesive pleuritis, basilar meningitis, tuberculous in type.

CASE 2. Mr. L., 28 years of age, entered the West Suburban Hospital in the care of Dr. K. M. Anderson. Three months ago while working long hours he had developed a severe "flu." Frequency and urgency followed. Pyuria was discovered. Three weeks ago he developed a progressively severe headache. Vomiting started 3 days ago.

He was muscular and well nourished. Temperature was 101°, pulse was 60 and respirations were 20. The pupils were equal and reacted normally. Papilledema was bilateral. No cervical adenopathy. The neck was stiff. Lungs were clear. Liver was just palpable. Spleen was not felt. External genitalia normal. Nodule felt in left lobe of prostate. Kernig's sign was positive. All deep reflexes reduced. Plantars normal.

The urine contained some pus. Blood leukocytes were 14,550; 88% neutrophils. The blood contained 53.5 mg. of urea, 4 mg. uric acid and 1.7 mg. of creatinine. Spinal fluid on admission: cloudy, under increased pressure, 785 cells, 80% neutrophils, Wassermann test negative, Pandy positive, many tubercle bacilli seen. Tubercle bacilli were also found in subsequent samples of spinal fluid. Repeated cultures of the spinal fluid yielded no other bacteria.

Roentgen ray showed miliary tuberculosis of the lungs.

Death occurred in the fifth week of his acute illness.

TABLE 1.—SPINAL FLUID IN 113 CASES OF TUBERCULOUS MENINGITIS

Age limits of patients	6 weeks to 58 years
Number under 10 years	66 (58%)
Number over 30 years	20 (18%)
Number with turbid or cloudy fluid	12 (10%)
Limits of cell count	30 to 3,000
Polys making 50% or more cells	12 (10%)
Polys only in	7 (6%)
Average number of cells	210
Number of cases with cells under 100	14 (10%)
Limits of total protein	20 to 712 mg.
Pandy positive in	112 of 113 tested (99%)
Leukocytes in blood below 10,000	39 of 59 cases counted
Levinson test	Negative 5 times in 16 cases so examined (31% error)
Tubercle bacilli found in	35 of 81 cases so examined (40%)

Summary. In tuberculous meningitis the spinal fluid may present all the gross and microscopic characteristics of "purulent" meningitis.

In 113 proved cases of this condition, the spinal fluid was cloudy in 10% and neutrophils constituted more than 50% of the cells in 10% of the cases.

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GASTRIC LAVAGE IN THE CONTROL OF TREATMENT OF PULMONARY TUBERCULOSIS*

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ALTHOUGH the presence of tubercle bacilli in the gastric contents was described in 1898,¹¹ gastric lavage as a diagnostic measure did not come into general use until the method was popularized by Armand-Delille only 15 years ago.^{1,2} It was originally introduced as a method whereby positive bacteriologic evidence of tuberculosis could be secured in the case of children who seldom raise sputum, but it was quickly recognized that the method was equally applicable to adults who did not expectorate.^{3,4,8,9,14} This represented a distinct advance, since it made a definite diagnosis possible in many previously doubtful cases.

* Read before a combined meeting of the Michigan and Wisconsin Trudeau Societies, June 12, 1942.

The reliability of gastric lavage as a diagnostic measure has been questioned on many grounds. Among these should be mentioned the possible presence of non-pathogenic acid-fast bacilli in the stomach contents, the possibility of contamination, and the relative value of direct smears, cultures and guinea-pig inoculations. In regard to the first question, Roper and Ordway,¹⁴ reporting a series of 1000 patients, found 2 with positive gastric lavages in whom they could demonstrate no evidence of pulmonary or visceral tuberculosis. In our series of 180 adults with positive lavages, in 1 case we were unable to demonstrate any lesion, despite numerous roentgenograms, bronchoscopy and nasopharyngoscopy to rule out the nasopharyngeal ulcerations described by Trenis.¹⁷ Subsequent lavages in this individual were negative. It must be recognized that when a proper technique is followed,⁵ the incidence of false positives is negligible. A previous study made by one of the authors¹⁹ has demonstrated the reliability of gastric lavage culture, and at the present time this method is used almost exclusively, although during the period covered by this report, culture and guinea-pig inoculations were done simultaneously on all specimens.

The question of the contagiousness of patients with a positive gastric lavage is frequently discussed. Ulmar and Ornstein¹⁸ demonstrated that, in the absence of cough, bronchial secretions are brought to the pharynx by a mechanism of bronchial peristalsis, and are then swallowed. If these bronchial secretions contain tubercle bacilli, the gastric lavage will yield positive results. The immediate significance of a positive lavage, therefore, does not differ from that of a positive sputum, and implies the existence of an open tuberculosis in communication with the bronchial system. Since the bronchial secretions of these patients contain tubercle bacilli, they are at least potentially infectious, and become actually so during periods of upper respiratory infections, with coughing or sneezing.

The objection is frequently made that gastric lavage is too sensitive a test for widespread clinical application. It has been claimed that the lavage will remain positive long after the lesions have become clinically inactive, or that it is unreasonable to insist on complete bacteriologic negativity, as manifested by repeatedly negative gastric lavage cultures, in patients who have had far-advanced disease with extensive cavitation.¹⁰ It has even been suggested that the lavage may be intermittently positive in such cases, even after effective collapse measures have been established. Since Stiehm¹⁶ has shown that the percentage of positive lavages will increase the more frequently they are repeated, some observers apparently feel that, if they are done sufficiently often, even healed lesions might yield positive results. The purpose of this investigation is to determine the relationship between the stage of the disease, the institution of collapse therapy and the results of gastric

lavage. In our series, gastric lavages were done on each of 2 consecutive days. Each specimen was separately cultured and inoculated into a guinea-pig, and a negative report was given only when both specimens were negative to all tests.

Following collapse therapy, cough and expectoration are frequently abolished. It would logically follow that, if the efficacy of collapse therapy is to be judged by its ability to remove tubercle bacilli from the bronchial secretion, examination of the sputum would be particularly inadequate in this group of patients. Because of inability to cough, these patients either raise no sputum at all, or the material which they do raise comes only from the upper air passages. Examination of such material, with a report of a negative sputum, tends to give the physician a wholly unwarranted confidence in the clinical status of the patient. In this group, therefore, gastric lavage would be of particular value in determining the efficiency of the collapse. However, there are only a few scattered references^{8,13,15} to the use of lavage for the control of collapse therapy.

To determine how long the lavage will remain positive after collapse has been established, the use of periodic gastric lavages as a routine measure in checking the clinical status of patients was introduced at Muirdale Sanatorium in March, 1939. During the 2 year period covered by this report, 491 adult patients were given a total of 1414 lavages at various stages during their treatment. Of this number, 180 patients (37%), at some time were found positive on lavage. These 180 positive lavages comprise the material on which this report is based.

TABLE 1.—DISTRIBUTION OF POSITIVE GASTRIC LAVAGES
Muirdale Sanatorium, March, 1939, to March, 1941

Group	Classification	Number	Total
O	No clinical evidence	1	1
I	Positive sputum and lavage	49	49
II	Sputum converted, lavage positive:		
	(a) Lavage converted	37	
	(b) Lavage still positive	28	65
III	Sputum negative, lavage positive:		
	(a) Lavage converted	20	
	(b) Lavage still positive	12	
	(c) Not repeated	21	53
IV	Sputum positive after lavage	12	12
		Total	180

To determine the clinical significance of the positive gastric lavages in these 180 patients, the results were divided into four main classifications (Table 1). In 1 case, as previously mentioned, no confirmatory evidence of tuberculosis was found. Group I consists of 49 cases in whom the positive lavages coincided with a positive sputum. In this group the sputum was usually negative on direct smear and concentrate. Lavages were done immediately, without

awaiting the results of sputum culture, which later proved to be positive. Although under these circumstances the lavage was merely confirmatory of the results of sputum examination, in many instances the bacilli were found in the lavage on smear, thus saving much time in establishing the diagnosis.

Group II consists of 65 patients who originally had positive sputa, but in whom the sputum subsequently became negative or absent. Despite the failure to find tubercle bacilli in the sputum, all were positive on gastric lavage. This group is of particular interest because it enables us to determine how long the gastric lavage can be expected to remain positive after the sputum has been converted. To determine this it was necessary to subdivide the group into: (a) those who became negative on lavage (37 patients), and (b) those in whom the last lavage was positive (28 patients). In Table 2 is shown the duration of positive lavages in this group. From the table it can be seen that, while in a few cases the lavage culture will be negative in less than 6 months, in the majority of cases from 12 to 18 months is required. In 1 case, with a bronchopleural fistula and tuberculous empyema, the lavage is still positive 5 years after the sputum became negative. Of the 37 patients whose lavages were converted while under observation, 62% were negative 18 months after sputum conversion, and 90% were negative within 2 years. This is an important consideration when the use of lavage for the control of collapse therapy is discussed, since, if negative lavage cultures are required before patients are discharged or permitted to take ambulatory pneumothorax, the period of sanatorium residence will be considerably prolonged.

TABLE 2.—DURATION OF POSITIVE LAVAGE AFTER SPUTUM CONVERSION

Months	Lavage converted after	Lavage positive after
0- 3	0	0
3- 6	3	2
6- 9	3	8
9-12	8 (40%)	8
12-18	9 (62%)	3
18-24	9 (90%)	3
24-	5	4
	<hr/> 37	<hr/> 28

Group III consists of 53 patients who never were positive on sputum examination, but in whom tubercle bacilli were discovered on lavage. In this group the lavage furnished the only positive bacteriologic evidence of tuberculosis. In 21 of these cases, the lavage was not repeated because the patients refused further lavage, left the institution or died. The remaining 32 cases were again subdivided, as in Group II, into: (a) those in whom the lavage was converted (20 patients), and (b) those in whom the lavages are still positive (12 patients). From Table 3 it can be seen that, in the

group with negative lavages, 75% were negative within 12 months and 95% within 18 months, as compared with 40% and 62% in Group II. As a rule, therefore, patients who have never had a positive sputum will completely heal their tuberculosis in an average of 6 months less than those who have been sputum-positive. This is to be expected, since it is merely a reflection of the fact that the gastric lavage will become positive earlier than the sputum, and thus permits diagnosis in a less advanced stage.

TABLE 3.—DURATION OF POSITIVE GASTRIC LAVAGE

Months	Lavage converted after	Lavage positive after
0- 3	1	2
3- 6	6	0
6- 9	4	2
9-12	4	1
12-18	4	3
18-24	0	2
24-	1	2
	<hr/> 20	<hr/> 12

This is well illustrated by the results in Group IV, 12 patients originally positive on lavage alone in whom the sputum subsequently became positive. This is an unfavorable sequence of events, indicating progression of the disease. Of the 12 patients in this group, 3 are dead and 4 have shown marked extension of their lesions.

In discussing the relationship of gastric lavage to collapse therapy, it was pointed out that, while negative gastric lavages prior to discharge were theoretically desirable, the prolongation of sanatorium care might be economically impractical, and the improvement in results might not warrant the additional expense. To obtain evidence on this point, a detailed study was made of the 57 cases in Groups II and III, who eventually became negative on lavage, to determine the exact relationship between the institution of an apparently effective collapse and lavage negativity. It was felt that in many instances the persistence of a positive gastric lavage might mean not so much a delay in healing time, as the necessity for supplementary measures, such as pneumonolysis, to render the collapse effective.

Of the 57 cases (Table 4), 7 were not given any form of collapse therapy. Of the remaining 50, 14 received phrenic paralyses, 24 were given pneumothorax, and 12 were subjected to major surgery, including thoracoplasty, extrapleural pneumothorax and paraffin pneumonolysis. In the entire group there were 16 minimal, 15 moderately advanced and 26 far advanced cases.

Of the 14 cases treated by phrenic nerve paralysis, 11 were minimal and 3 moderately advanced. The interval between the phrenic nerve interruption and negative gastric cultures varied from 2 to

25 months (Table 5), averaging 8 months for the entire group. In 11 of the 14 cases, negative lavages were obtained in less than 9 months. Of the remaining 3, 1 had not been lavaged for the preceding 7 months, and the other 2, both minimal cases with fibroid apical lesions remained positive for 25 months. If these 2 are excluded, the average for the entire group is only 6 months.

TABLE 4.—CLASSIFICATION AND TREATMENT IN CONVERTED LAVAGES
(Groups II and III (a), 57 Cases)

Treatment	Minimal	Moderate	Far	Total	Average interval
Routine . . .	3	3	1	7	?
Phrenic . . .	11	3	..	14	6 mos. ¹
Pneumo. . . .	1	9	14	24	10 mos. ²
Surgical . . .	1	..	11	12	9 mos.
	<hr/> 16	<hr/> 15	<hr/> 26	<hr/> 57	

¹ Excluding 2 cases, each 25 months.

² Excluding 4 cases, 27, 29, 37, 45 months.

TABLE 5.—INTERVAL BETWEEN EFFECTIVE COLLAPSE AND NEGATIVE LAVAGES
(50 CASES)

Months	Phrenic	Pneumo.	Surgery	Total	%
0-6	7	8	5	20	
6-12	4 (80%)	6 (60%)	3 (66%)	13	66
12-18	1	2	3	6	80
18-24	4 (90%)	1	5	86
24-	2	4	..	6	
	<hr/> 14	<hr/> 24	<hr/> 12	<hr/> 50	
Total	14	24	12	50	

The pneumothorax group consisted of 1 minimal, 9 moderately and 14 far-advanced cases. Many of these had bilateral lesions, which in some instances, made evaluation of the effectiveness of unilateral collapse difficult. When supplementary measures, such as pneumonolysis, were necessary to convert an ineffective pneumothorax into an effective collapse, the interval between the establishment of effective collapse and lavage negativity was determined, and was found to range from 1 month to 45 months. Of this group, 60% were negative in less than 1 year, and 90%, or all but 4, were negative within 2 years. In every one of these 4, far-advanced bilateral disease was present. If these 4 are eliminated, the average interval for the remainder of the group was 10 months.

With the exception of 1 minimal case, in which a paraffin pneumonolysis was done, all of the patients submitted to major surgery had far-advanced disease. Despite this fact, the interval from completion of the surgery to negative lavage cultures ranged from 1 to 22 months, averaging 9 months. This interval, which is less than that for patients treated by pneumothorax, shows the great effectiveness of surgical collapse of advanced disease, and is in sharp opposition to the prevalent opinion that, in such cases, a requirement of negative lavage cultures prior to discharge is unreasonably strict.

Table 5 summarizes the results in the entire group of 50 patients treated by collapse therapy in whom the gastric lavage was converted; 66% were negative in 1 year, 80% in 18 months and 86% within 2 years (in a group of patients consisting of 26% minimal, 24% moderately advanced, and 50% far-advanced cases). These results indicate that the gastric lavage tends to remain positive until adequate collapse has been established, and thereafter becomes negative when sufficient time has elapsed to allow complete healing. Far from being too sensitive, it is the most reliable laboratory evidence we have of the clinical status of the individual patient. It is more reliable than the sputum examination, and particularly in the group treated by collapse therapy, is an indispensable measure in evaluating the results.

Summary. 1. In a group of 491 adult patients with tuberculosis, a total of 1414 gastric lavages was done. Of this number, 180 patients (37%) were positive on at least one examination.

2. An analysis of these 180 patients with positive gastric lavages is presented.

3. The duration of a positive lavage after the sputum has become negative was determined in 57 cases. In 90% of this group, the lavage cultures and guinea-pig inoculations were negative in less than 2 years, and averaged 11 months for the entire group.

4. In a group of 50 patients treated by collapse therapy, 86% were negative to gastric lavage culture and guinea-pig inoculation in less than 2 years, with an average interval of 8.5 months.

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SUCCESSFUL REMOVAL OF HEMANGIOMA OF THE LUNG FOLLOWED BY THE DISAPPEARANCE OF POLYCYTHEMIA

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THE rarity of hemangioma of the lung may be judged from the fact that no previous case has been encountered by the pathologic department of this hospital. It is not surprising, therefore, that a search of the literature has yielded very few reports describing the occurrence of such a lesion. This has led us to report the following case in which the diagnosis was made on the basis of clinical and laboratory findings and which is, so far as we are aware, the first reported case in which a cure was brought about by pneumonectomy.

Cavernous hemangioma of the lung is not mentioned in Henke and Lubarsch's Handbook of Pathology.⁶ This work, however, does refer to a case described by de Lange and de Vries-Robles² (1923) of an infant aged 2½ months, whose lungs, at autopsy, were seen to contain 2 small tumors, which microscopically were shown to be capillary hemangiomas. Wollstein⁹ in 1931 reported a malignant hemangioma of the lung which was found at autopsy in a child aged 4 months, and Hall,⁵ in 1935, also described a malignant pulmonary hemangioma in a woman aged 40. In both these malignant cases there was a distinct anemia and an appreciable lowering of the red blood count. Bowers,¹ in 1936, reported the death of a new-born child, caused by hemorrhage from a ruptured pulmonary hemangioma. In 1939, Duvoir *et al.*³ related the case of a child who, from 1932, had been subject to paroxysms of dyspnea and who had congenital lues. Roentgen ray films of the chest showed an opacity which was thought to be caused by a lipoma. Pathologic examination of the removed tumor, however, showed the mass in the lung to be a hemangioma. The child died of pneumonia 5 years later and autopsy revealed many lipomata, visceral angiomata and 1 lipoangioma. Cyanosis and clubbing of the fingers were not mentioned and no blood examination was recorded.

Rodes,⁷ in 1938, described a case of hemangioma in which there was a polycythemia and stated that he could find no previous record of polycythemia arising from such a cause. This patient had been cyanosed and dyspneic for as long as he could remember. Clubbing of the fingers was noted when he was 15, and clubbing of the toes appeared 8 years later. In 1935, when he was 25, the cyanosis and dyspnea were more marked and hemangiomata appeared on his lips. His heart was normal in size and shape and

showed no evidence of congenital defects; the spleen was not palpable. The hemoglobin varied from 108 to 118%, and the red blood cell count was 7.2 to 7.5 million cells per cmm. In May, 1936, he had a sudden hemoptysis and died 6 days later from repeated bleeding from the lung. Autopsy showed 2 hemangiomata in the right and 1 in the left lung.

In November, 1939, Smith and Horton⁸ reported the case of a man, aged 47, with polycythemia associated with an arteriovenous fistula in the lung. This patient had been a "blue" baby, and cyanosis and clubbing of the fingers had been noted by an Army physician when he was 23 and were observed again 17 years later at the Mayo Clinic. The spleen was not palpable and the patient showed no evidence of congenital heart disease. His hemoglobin was 20.6 gm. per 100 cc.; the red blood count varied from 5,440,000 to 6,220,000 per cmm.; the total blood volume was increased (figures not given). At that time the patient was thought to have atypical polycythemia rubra vera and was treated by phenylhydrazine and venesection. In 1938, after many venesections and having taken a considerable amount of phenylhydrazine, his condition was relatively unchanged. The cyanosis and clubbing were still marked. The blood findings—red blood count 6,470,000, hemoglobin 23.7 gm. per 100 cc., and blood volume 121 cc. per kg.—were even more characteristic of polycythemia vera. At this time, however, a continuous bruit was heard in the region of the base of the right lung. Roentgen ray examination of the chest showed some infiltration of the lung in this area, which at first was thought to be bronchiectatic. However, Roentgen ray films after the injection of a radiopaque medium into the basilic vein showed two dilated vessels arising in the right hilum and communicating in the parenchyma of the right lung where the bruit was heard. The final diagnosis was arteriovenous fistula of the right lung.

Case Report. Mrs. J. S., aged 23, was admitted to this hospital for the second time in January, 1940, complaining of an attack of dizziness, faintness and thick speech. The patient had never been robust and, in 1932, at the age of 15, had been put to bed with the diagnosis of "a leaking valve." Clubbing of the fingers was first noted at that time. Following this she became aware of shortness of breath on climbing one flight of stairs. In 1937, on the occasion of a pelvic operation, her hemoglobin was found to be 91% (14.2 gm. %) and the red blood count 6.3 million per cmm. In 1938, because of chest symptoms, she was sent to the Muskoka Hospital for Tuberculosis where clubbing of her fingers was again noticed and, in addition, cyanosis was observed. The hemoglobin at that time was reported to be only 78% (12.2 gm. %). Roentgen ray examination of the lungs revealed an infiltrating process in the right middle and lower lobes which was shown by lipiodol injection not to be bronchiectatic. The patient was transferred to this hospital in May, 1938, with the following statement from Dr. C. B. Ross of the Muskoka Hospital: "The lung condition is either a fibrosis giving a rather unusual clinical picture or something in the nature of a vascular endothelioma." On this, her first admission to this hospital, slight generalized cyanosis, clubbing of the fingers, and some

suppression of the breath sounds medial to the vertebral border of the right scapula were noted. Her heart was not enlarged and presented no murmurs. The spleen was not palpable. The hemoglobin was 95% (14.8 gm. %); the red blood count 4.7 million per cmm. The patient did not wish to submit to bronchoscopic examination and so left hospital without further investigation, the provisional diagnosis being pulmonary fibrosis.

During the next 18 months she became more dyspneic, more cyanosed and more easily tired. In January, 1940, she was seen by one of us because of an attack of dizziness, faintness and thick speech—symptoms similar to those described by Smith and Horton⁸—and she was readmitted to this hospital.

On this second admission, in addition to the rather marked cyanosis and clubbing of the fingers, there was some diminution of movement and of lung resonance in the right scapular region but no bruit was heard. The heart was not enlarged and there were no cardiac murmurs. The spleen could not be felt. Blood examination showed a marked polycythemia, the hemoglobin being 140 to 146% (21.8 to 22.8 gm. per 100 cc.), and the red blood count 9 to 9.6 million per cmm. The packed cell volume was 80%. The total blood volume was raised to 8500 cc. (normal is 3500 cc.). The vital capacity was 1700 cc. Fluoroscopic and Roentgen ray examinations demonstrated a shadow in the right middle and lower lobes, similar to that previously noted at the Muskoka Hospital.

It was felt that the cyanosis which the patient exhibited was not secondary to the polycythemia since it had been present before any increase in red cells or hemoglobin had occurred and was central rather than peripheral in origin. That this was true was shown: first, by the observation that when the patient's hand was immersed for 10 minutes in a water bath at 45° to 47° C. it became uniformly and more deeply cyanosed; and second, by the fact that arterial blood, obtained from the femoral artery and also from the veins of the heated hand by the method of Goldschmidt and Light,⁴ was only 70 to 75% saturated with oxygen (normal saturation is 95%).

The possible causes for such an arterial oxygen unsaturation were: (1) a congenital heart lesion; (2) a generalized pulmonary condition, such as Ayerza's disease, in which none of the blood leaving the lungs is properly aerated; (3) a local lung condition allowing by some means, such as a shunt, the passage of a proportion of blood directly from pulmonary artery to pulmonary vein. As this patient presented no evidence of congenital heart disease and no suggestion of any generalized pulmonary disease, and as she did show a circumscribed local lesion in the lung on Roentgen ray examination, it was felt that she probably had an abnormal arteriovenous communication in the lung in the nature of a cavernous hemangioma. The cyanosis could then be adequately accounted for and the other signs and symptoms (dyspnea, dizziness, fatigue, polycythemia and clubbing of the fingers) could be considered as secondary manifestations of the resultant anoxemia.

An attempt was made by artificial pneumothorax to close this arteriovenous communication in the lung but, although a good collapse was obtained, no change could be noted in the degree of cyanosis and no increase occurred in arterial oxygen saturation (Table 1). Pneumonectomy was then performed by Dr. N. Shenstone and Dr. R. Janes on February 14, 1940. The details of this operation will be reported by them elsewhere.

At operation, when the right lung root was clamped it was found that the cyanosis disappeared promptly. The exposed lung showed a cyanosed mass occupying the upper part of the right lower lobe. This was removed along with the whole of the right lung. The patient was very uncomfortable for a few days but within a week she was sitting up in bed, all signs of cyanosis having disappeared and her complexion now a rosy pink.

Examination of her arterial blood at this time showed it to be normally saturated with oxygen (Table 1). Prompt disappearance of polycythemia was accounted for, at least in part, by the occurrence of a large hemothorax and by the loss of blood at operation. The patient was allowed out of bed at the end of 6 weeks and was discharged from hospital 2 months after her operation.

TABLE 1.—BLOOD FINDINGS

Date, 1940	Hemoglobin, %	R.B.C., m. per c.mm.	Arterial blood		
			O ₂ content, vol. %	O ₂ capacity, vol. %	Saturation, %
21/1	140	9.4	21.6	29.6	73.0
23/1	138	9.0	22.3	29.9	74.5
<i>After Pneumothorax</i>					
6/2	135	8.3	21.3	29.6	72.0
<i>After Pneumonectomy (Feb. 14, 1940)</i>					
23/2	93	5.4	18.4	19.3	95.3
17/4	73	4.4			
1941					
25/4	71	4.3			

The pathologist's report on the lung removed at operation reads, in part: "Involving the mid-portion of the lower lobe is a large angiomatous mass, roughly measuring 8 x 6 x 4 cm., made up of cavernous sinuses linked up with one another. Some of the caverns measured up to 1.5 cm. in diameter. The lining of these sacs was smooth and greyish-white in color. On sewing up the cut surface of the lung and injecting one of the branches of the pulmonary artery this angiomatous mass was distended." The pathologic diagnosis was "cavernous angioma of the lung."

Ten days after discharge the patient was feeling well and exhibited no sign of cyanosis. The clubbing of her fingers was less marked and a long-standing acne-like eruption on her face had vanished. She was less tired and her exercise tolerance had greatly increased. In September, 1940, 7 months after operation, she showed further improvement both subjectively and objectively. In March, 1941, she reported that, although 6 months pregnant, she was more fit than she had ever been, that there was no return of the cyanosis, and that all clubbing had disappeared except from one thumb. By the end of April, 1941, all the clubbing had entirely disappeared, she was looking and feeling well, the pregnancy was progressing normally, and the only abnormality found on blood examination was a mild degree of secondary anemia.

Summary. The case reported is one of cavernous hemangioma of the lung. This pathologic defect allowed the flow of a considerable volume of unoxygenated blood directly from the venous to the arterial circulation which resulted in a marked cyanosis of central origin with secondary manifestations of clubbing of the fingers and a true secondary polycythemia. When the patient was seen by us in January, 1940, diagnosis was relatively easy: polycythemia, cyanosis not due to peripheral stagnation, absence of signs of congenital heart disease, and an infiltrating lesion of the lung could only be accounted for by such a lesion. Great credit is due to Dr. C. B. Ross of the Muskoka Hospital for suggesting the diagnosis of vascular endothelioma of the lung before the development of polycythemia.

Removal of the hemangiomatous pulmonary growth was accomplished without any particular difficulty by the surgical division. This was followed by an immediate cessation of cyanosis, by a rapid decrease in the polycythemia, by a more gradual disappearance of clubbing of the fingers and, after a short period, by a definite increase in general health and sense of well-being.

We wish to thank Professor Duncan Graham for permission to report this case.

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SINGLE COMBINED TREATMENT FOR GONORRHEA

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THE value of the sulfonamides in treatment of gonorrheal urethritis is well established. However, cure rate has not reached 100% regardless of the derivative of the drug used. The percentage of cases which have failed is from 10 to 40%, according to the drug employed and the method used. These cases which underwent an intensive course of sulfonamide and failed have been treated in many ways, such as repeated courses of sulfonamides, irrigations, typhoid vaccines, gonococcus vaccine and fever therapy.

Fever therapy in the treatment of active gonorrheal urethritis was initiated by the Kettering Institute for Medical Research. Carpenter, Boak, and Warren⁷ found the rationale of such therapy in working out the thermal death time of various strains of gonococcus. The lethal temperature ranged around 106° F. for a duration of 6 to 24 hours. Several investigators compiled statistics in the use of fever therapy alone for treatment of gonorrhea.

With the advent of sulfanilamide, physicians began to combine this drug with fever therapy. Ballenger and Elder,¹ for instance, using ordinary dosages of sulfanilamide and 3 fever sessions averaging 4 hours on alternate days at temperatures up to 104° F., claimed

that 100% of the cases were cured. Later (1939) they reported a cure rate of 90% on a larger series of cases. Owens, Wright and Lewis⁵ administered sulfanilamide for 4 days followed by 10 hours of 106° F. and reported almost 100% of them as being cured. Belt and Falkenberg,² using sulfanilamide for 7 days, 5 hours of fever therapy at 106° F. on the 3d, 5th and 7th days, reported 86% of 49 cases as being cured. Kendall, Simpson and Rose⁶ claimed 100% results in 31 cases, using the combination of sulfanilamide and fever.

In an endeavor to improve the treatment of gonorrhea by speeding recovery, we carried out the following clinical study. The plan was to develop a high concentration of sulfathiazole in the patient, then subject him to hyperpyrexia. If one such treatment would prove effective, time can be saved for the patient and the public health problem simplified.

Selection of Cases. Our cases are all seamen with an age range of from 19 to 47 years who have picked up various gonococcal strains from many countries bordering on the sea. The number of previous infections per patient varied from 0 to 5. The duration of infection was from 1 to 60 days. Most of the cases were uncomplicated. The few that had acute gonorrheal epididymitis are so listed.

All the patients on entry to the hospital were given a physical examination and a history was taken. Smears and cultures were taken to confirm the diagnosis.

Procedure. The patient is given 1 gm. of sulfathiazole starting at 2 P.M. the day before the fever therapy and continued every 4 hours until a total of 5 gm. are administered. The man is then given an enema and, following this, a hot tub bath which brings the surface temperature to about 102° F. The patient is then put into a preheated fever cabinet and his temperature slowly raised until 106° F., by rectum, is reached. This takes about 1 hour. This temperature is maintained for about 7 hours. During his stay in the hypotherm cabinet the patient is given, by mouth, from 3 to 4 liters of normal saline, flavored with Karo syrup. Following this treatment the patient is warmly wrapped in blankets, brought to his room and given fruit juices and milk for the next 24 hours.

Criteria of Cure. The criteria of cure included complete cessation of all objective symptoms, disappearance of discharge and dysuria and clear urine in the 2 glass test. Bacteriologic and cultural examinations were done on all patients in the following manner: Starting on the 2d day after fever therapy and on subsequent 2d or 3d days thereafter for 3 times, the patient was sounded, his urethra massaged gently against the sound and the sound removed. A prostatic massage was next done for microscopic and cultural examinations of strippings. Three consecutive negative cultures were required before the patient was discharged.

Data. Table 1 shows the results of the combined therapy given to the uncomplicated cases of gonorrhea.

TABLE 1.—RESULTS OF COMBINED THERAPY IN UNCOMPLICATED CASES

Previous treatment	No. of combined treatments	Patients	Cures	Failures	% cures
None*	1	25	22	3	88
Sulfathiazole (20 gm.),† 8 days	1	20	18	2	90
One course of sulfonamide† plus sulfathiazole (20 gm.), 8 days	1	26	22	4	85
One course of sulfonamide† plus sulfathiazole (20 gm.), 8 days	2	4	2	2	50
Total	—	75	64	11	85.3

* Duration of disease of those cured, 3 to 30 days; those who failed, 5 to 8 days.

† Period of rest between treatments, 3 to 10 days.

Two cases of acute gonorrhea accompanied by epididymitis were given one course of sulfathiazole and failed to respond. These patients then received the combined treatment which resulted in a cure of each.

Comment. We have found several interesting factors in our study. It would appear that duration of illness has no bearing on the efficiency of the combined sulfathiazole and fever therapy. Success has been obtained in cases with a duration of as short as 3 days.

In this series, the combined therapy of sulfathiazole and hyperpyrexia successfully cured 85.3% cases of gonorrheal urethritis. Necessity of a rapid cure is the chief indication. It is of distinct advantage when previous treatment has failed.

The treatment should be confined to the young and vigorous, as it is drastic. The most annoying complications are herpes about the face as a result of the heat. Some patients suffer malaise and weakness for 2 to 3 days. A disadvantage is the expense, as a nurse's constant attention is required as well as relatively expensive apparatus. Large doses of the sulfonamides are not without risk and harm as we have cautioned in previous publications.³ We recently had one patient develop anuria from 300 gr. of sulfanilamide, given at a rate of 80 gr. per day. No calculus or mechanical block was involved. He was anuric for 8 days, then recovered. French⁴ has called attention to an interstitial myocarditis that may result from these drugs.

Conclusion. Of 75 cases of uncomplicated previously untreated gonorrheal urethritis, treated with sulfathiazole 5 gm. for 18 hours prior to fever therapy of 7 hours of 106° F., 88% were cured (22 of 25). Of those receiving this therapy after one course of sulfonamide, 90% were cured (18 out of 20). Of those receiving this therapy after more than one course of sulfonamide, 85% were cured (22 of 26). Of 2 cases of epididymitis not included in this list, both recovered after one treatment of the combined therapy.

The chief indication for this type of therapy is the necessity of a rapid cure for selected patients.

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BLOOD PRESSURE AND SULFOCYANATES (THIOCYANATE)

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SULFOCYANATES are naturally present in the body in a much higher concentration than any other known depressor substances. Although for many years nitrites have been the depressor substances of choice in the treatment of hypertension, the natural blood concentration of sulfocyanates is approximately 50,000 times that of nitrites.

In our studies, the natural concentration of blood sulfocyanates in 241 persons to whom the drug had never been administered ranged from 0.31 to 2.55 mg. per 100 cc. of blood. In the groups of individuals whose pressure was in the normal range, the blood sulfocyanate concentration averaged 1.2 mg. per 100 cc. of blood.¹

Each individual has a fixed natural blood concentration of sulfocyanates that does not change appreciably from week to week. Of 29 unselected persons who had never taken sulfocyanates, picked at random without regard to blood pressure or other factors, the initial blood concentrations ranged from 0.36 to 2.04 mg. per 100 cc. of blood. Repeat determinations, made from 1 to 2 weeks later, showed no variation in 3; variation of 0.10 mg. or less in 15, and a mean variation for the 29 of 0.14 mg. per 100 cc. of blood.¹

The constancy of the blood concentration of sulfocyanates is quite marked not only in the subjects we have studied, but also in patients to whom sulfocyanate has been administered for therapeutic effects. While different individuals vary greatly in their reaction to the

drug, each person tends to show a very constant level after becoming adjusted to the influence of the drug.

Studies of 241 individuals who had never received sulfocyanate therapy indicate that blood pressure varies in inverse ratio to the blood sulfocyanate concentration.⁴

For analytical purposes in this work, we have classified blood pressure readings as follows:

Below 106 systolic: hypotension

106 to 130 systolic: normal pressure

131 to 140 systolic: borderline

141 and above systolic: hypertension.

Diastolic pressures have been classified similarly, diastolic readings being expected to be approximately two-thirds of the above readings. These figures are in keeping with the published work of the Association of Life Insurance Medical Directors and The Actuarial Society of America, which places 128 mm. as the maximum normal systolic pressure and 84 mm. the maximum normal diastolic pressure.²

The averages of blood sulfocyanate concentrations for each blood pressure group make definite curves for systolic and diastolic pressures. Also, all cases presenting high blood pressure fall in the low sulfocyanate concentration group; while in the high blood sulfocyanate group, no hypertension cases appear. Above a blood concentration of 1.54 mg. no diastolic pressures above 90 mm. were found, and the only systolic pressures above 130 mm. were one of 150 mm. and one of 138 mm.

All of our studies have been made on blood serum. Barker and others have made exhaustive studies of the sulfocyanate content of various body tissues and fluids. Sulfocyanates are present in all parts of the body, though some tissues contain much more than others.

Many vertebrates are known to have sulfocyanates present in considerable amounts throughout their bodies; no vertebrates are known to be without it.

Blood Pressure Studies. As described in earlier reports of this work^{1,3} every effort has been exerted to assure results that would not be influenced by variations in diet, exercise or other factors. Accordingly, every person admitted to the State Prison and to the State Hospital for the Insane was studied. Samples of blood were collected on the second morning after admission before breakfast and before tobacco was used. All subjects were at rest in the institutions for observation and general study and appraisal. There was reasonable similarity of diet for all individuals in both institutions. Apparently we had as exact a control over the environment, diet and activities of the subjects as was possible. Studies were made of 241 consecutive admissions.

To secure maximum accuracy in the study, all determinations were made by a graduate student in chemistry, using an Evelyn

photoelectric colorimeter.^{4,6,7,8} Tests showed that a filter of wave length 440μ was correct for this work. Blood serum was used for the tests. As a further check on accuracy, recovery tests by silver nitrate precipitation were made and indicated that the results were well within the acceptable limits of technical error.

Similar studies on a large number of other persons in private life have been made. These show the same very definite inverse ratio of blood sulfoeyanate concentration to blood pressure. However, since they were not under such strictly controlled environment, they have not been included in our statistics (Chart 1).

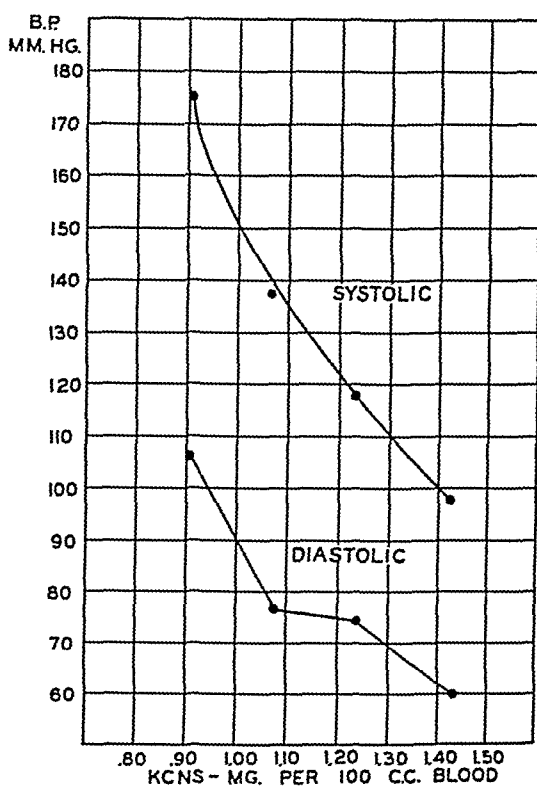


CHART 1.—Results of sulfoeyanate studies on prisoners at the State Prison. This shows the inverse ratio between blood sulfoeyanate concentration and blood pressure levels.

Pressor Substances. In the human body there appears to be a delicate balance of control over blood pressure. There is a pressor substance that is associated in some way with the adrenals and perhaps also with the kidneys. The normal tonicity of the arteriolar musculature is maintained by elastic tissue and the action of the pressor substance on the muscular coat. In Addison's disease there is a deficiency of this pressor substance and blood pressure is low. Undoubtedly, epinephrine plays a very important rôle in the

maintenance of tone in the vessel walls whether low, normal, or high pressure exists, and epinephrine has been generally accepted as the essential pressor substance. Occasionally a tumor of the adrenal gland is seen, such as the paraganglioma, in which severe rises in blood pressure occur but may be relieved by removal of the tumor or the adrenal.^{9,11,13}

In some cases of hypertension there appears to be an excess of pressor substance. There are also depressor substances in the body which help to counterbalance the effects of the pressor substance. Nitrites, present naturally in minute amounts,¹⁰ have been used as depressor substances for many years. Sulfocyanates are the only known depressor substances present naturally in the body in appreciable amounts and they exert very satisfactory depressor effects on blood pressure at any level. Our work has shown that low blood pressure is likely to be associated with a high blood sulfocyanate concentration, that high pressure is associated with a low blood sulfocyanate concentration, and that normal and borderline pressure cases occupy intermediate positions. It is especially noteworthy that higher concentrations of sulfocyanates are not associated with hypertension.

Blood Pressure Control. The whole story of blood pressure control cannot be found in either pressor substances or sulfocyanates alone. There is a delicate balance of control between the two substances and either may be present in the body in excess, in normal amounts, or be deficient; and any combination of these states is also possible. This is well illustrated by the fact that in many patients hypertension may be corrected without raising the blood sulfocyanate concentration above normal natural levels, while other cases require that they be stabilized at a high concentration; *i. e.*, enough sulfocyanate must be kept in the blood stream to counterbalance an excess of pressor substances.

Sulfocyanates appear to act efficiently in the reduction of blood pressure of any level, whether the pressure be high, low, normal or borderline. Unless too much change in the arterioles and capillaries has occurred there appears to be very little restriction on the degree of reduction that is possible.

The usual approach in the treatment of hypertension is on the plane of control of symptoms; only relatively rarely is one able to discover basic causes for the condition. Relief of symptoms is of definite value to the patient but unless the pressure is lowered there can be only symptomatic relief.

The control of blood pressure is further complicated by other etiologic factors. We attempt to eliminate all cases that represent a physiologic rise in blood pressure due to emotion or exercise and in which the rise in blood pressure is the result of increased cardiac output; such rises are transient and we do not classify them as hypertension. The sustained elevations of pressure resulting from

increased peripheral resistance to the blood flow represent pathologic hypertension and it is with this type of cases that we have been working.

Many substances will reduce systolic blood pressure temporarily. Most of this relief is psychic in nature. The attitude and manner of the attending physician may raise or lower pressures. Pressures may rise 50 points or more in patients with hypertension due to careless remarks by the physician. But unless drugs lower the diastolic pressure as well as the systolic pressure, there is little or no benefit for the patient.

Nitrites are typical of the large group of drugs that lower systolic pressure temporarily; but the diastolic pressure is not lowered satisfactorily and systolic improvement is not likely to persist very long. A satisfactory depressor substance must relieve spasm of the arterioles, thereby lowering the diastolic pressure. After hypertension has persisted for a long time and arteriolar spasm has been replaced by arteriolar sclerosis with calcification, relaxation is no longer possible and it is doubtful if any treatment other than symptomatic is feasible.

Treatment. This raises the point as to the proper time at which to institute treatment for hypertension. An average normal blood pressure may be assumed to be 120/80. Any rise above normal is likely to be gradual rather than sudden. At some point in this rise, treatment should be instituted. The longer treatment is delayed and the higher the pressure is allowed to rise before treatment is begun, the more likely are the arterioles to become sclerotic or calcified and the less satisfactory must be the results of treatment. If a pressure that tends to rise can be returned to normal in the early stages, there is a good possibility of preventing anatomicopathologic changes; when such changes progress sufficiently far, they are irreversible.

In older persons, who have become accustomed to high pressure, especially if there be arteriolar sclerosis, caution must be observed in lowering pressures from any level.

In the beginning of studies to appraise hypertension, each patient should have a thorough study to discover and correct all possible factors that might influence the picture. Allergy, faulty digestion, hyperthyroidism and many other conditions may occasionally produce or intensify hypertension. Such conditions should be corrected and time allowed for improvement before any specific methods of treatment are instituted.

Bed rest may be necessary in the beginning of treatment because of vascular crises, threatened cardiac decompensation or other complications; otherwise, better results are obtained by avoiding too much bed rest: it has a bad psychologic effect on the patient. Early in the treatment, some rest may be indicated at various times during the day, but this is largely symptomatic treatment

and must be applied to the individual patient along with other general measures.

We use small doses of mild sedatives almost routinely in the treatment of hypertension. Our usual procedure is to give 0.5 gr. phenobarbital on rising and at noon daily. This takes the edge off the patient's nerves during the day and permits more satisfactory sleep during the night; by not giving sedatives at bedtime, there is less likelihood of a hangover the next morning. It is doubtful if worry and stress and strain are responsible for hypertension. However, patients with hypertension do worry excessively and are likely to live under high stress and strain. A small dose of sedative aids in the treatment. Frequently, especially in milder cases of hypertension, the sedative can be reduced or stopped after a few weeks as the pressure approaches normal.

Diet. A minimum of stress is placed on the kind of diet. The amount of food taken is of far greater importance than the selection of the diet. Overeating appears to play an important part in the maintenance of pressure at a high level. We attempt to keep body weight as nearly normal as possible.

Almost all patients will show some drop in blood pressure on this regimen. After this has been followed until we are sure that no further improvement is to be expected, sulfocyanates may be given if the pressure is still too high. In this way, we have attempted to eliminate the danger of crediting psychic improvement to sulfocyanate therapy.

Sulfocyanate Therapy.—The potassium salt appears to be the form best suited for sulfocyanate therapy. It is not toxic in therapeutic doses, and it is given in larger doses than the sodium salt. As an initial dose we give 5 gr. daily, best given after breakfast. We do not give sulfocyanate to patients unless we are sure of securing a reasonable degree of coöperation.

This drug shows no tendency to the development of tolerance to its action. But there is a cumulative effect in many cases. For protection against this effect we make frequent determinations of the blood sulfocyanate concentration.^{2,12} It is noteworthy that as the blood concentration of potassium sulfocyanate rises, blood pressure falls. At the beginning of its administration weekly blood tests appear to be adequate. Later, as the patient's response to the drug is better known, tests are made less frequently and still later at monthly intervals. We find that the lower the effective blood sulfocyanate concentration can be kept, the better the results. Many of our patients do best with a concentration of potassium sulfocyanate in the blood of 2.5 to 3 mg. per 100 cc. of blood which is within or near natural levels found without sulfocyanate therapy. Other patients require a concentration of 5 to 8 mg. or more per 100 cc. of blood. We use the lowest concentration that yields required results. No maximum concentration has been set, though

20 mg. per 100 cc. of blood is usually accepted as a high safe range. We have observed concentrations of 40 and 65 mg. per 100 cc. of blood with no serious ill effects. However, it appears that death may be produced at lower levels. To avoid untoward symptoms, pressures must be reduced slowly and gradually. The effects of sulfocyanates develop slowly and persist for a considerable time after therapy has been stopped. Frequently it is necessary to reduce the dose. Occasionally after several weeks it is necessary to increase the dose above 5 gr. daily. We have observed that with improvement in blood pressure and symptoms dosage may be reduced gradually after weeks or months of treatment.

The essential factor in treatment of hypertension is to furnish a sufficient amount of sulfocyanate to balance an unknown amount of pressor substance and maintain blood pressure at a satisfactory level. This level must depend on the degree of change in arterioles and capillaries, the cardiac reserve, and pressor substances.

Dangers. No contraindications to the use of sulfocyanates have been found. However, we always use it with care, especially in old arteriosclerotic patients. We do not expect to reduce extremely high pressures of long standing to normal levels. Such cases will require somewhat higher pressures than normal for at least several months. However, we find that almost every case will show a slow gradual fall over a period of several months. In angina pectoris, associated with hypertension, sulfocyanates can be used with care. A moderate and slow reduction of pressure tends to relieve angina. Sulfocyanates produce a prolonged effect instead of the fleeting effects of nitrites and demonstrate their superiority by reducing diastolic as well as systolic pressures.^{2,5,12}

In cardiac decompensation we do not use sulfocyanates until compensation has been restored by rest in bed and such supportive measures as may be indicated. Then sulfocyanates are indicated. Cardiac decompensation is likely to appear in patients who have presented very high diastolic pressures.

In these cases, the heart has little opportunity to rest. The increased cardiac load results from increased peripheral resistance which in turn raises the diastolic pressure. Cardiac decompensation and failure are responsible for more than half the deaths of hypertensive patients. A lowered diastolic pressure makes recurrences of decompensation less likely. In apoplexy even slight lowering of the pressure tends to reduce the danger of recurrences.^{2,3,5}

It has been noteworthy that in the sulfocyanate treatment of hypertension there is no tendency toward increased nitrogen retention in the blood. The assumption that sulfocyanates improve the circulation in the kidneys, especially in efferent vessels, has some justification.

Discussion. Sulfocyanate treatment is recognized as substitution therapy. It supplies sulfocyanate to a group of individuals who

suffer from high blood pressure and who also as a group have less sulfocyanate in the blood than other individuals.⁴ The treatment apparently will be required for life.

Best results are obtained in less severe cases. Treatment should be started before there is too much sclerosis of the arterioles. Relief in hypertension by any method is possible only to the extent that spastic or sclerotic arterioles can be made to relax. After there is too much sclerosis there is grave doubt as to whether relaxation is possible.

Results. In our clinic in the past 4 years we have had a total of 136 hypertensives who have continued the treatment as long as 3 months. Shorter periods of treatment do not appear to be adequate for appraisal of the value of results. Symptomatic improvement seems to satisfy some patients and cause them to stop treatment. During the past 2 years, we have used smaller blood concentrations of sulfocyanates and have secured better results than formerly with higher concentrations.

We expect to get relief of symptoms in practically all cases. Functional results are good in two-thirds, while one-third show poor or fair results from treatment. Proper selection of cases for treatment would increase the percentage of good results almost to 100%. We feel that we are not justified in making such a selection because of the benefit from fair results and also from symptomatic improvement.

The underlying factor in failure is fibrosis of the arterioles and capillaries; this is seen in old arteriolar sclerosis itself as well as in syphilis, hemiplegia and cardiac decompensation. Fair results may be obtained in many of these cases by prolonged treatment. Difficulties have also been encountered in handling toxemias of pregnancy by this means.

Of our cases, 92 (67.7%) have been classed as showing good results, *i. e.*, showing a sustained reduction of at least 15% in both systolic and diastolic pressures (Table 1). Better results are obtained in private patients than in clinic and institutional cases (our private cases show 79% good results and 7% fair results) due to less syphilis, less vascular sclerosis, earlier diagnosis and treatment, and also to better coöperation. A large number of our cases show more than 15% reduction in pressures, many cases showing a normal pressure after some months. While 15% reduction is not dramatic, it is sufficient to relieve symptoms and decrease the danger of hemiplegia and angina.

There have been no deaths among our patients who were on treatment, or who had been on treatment. There has been 1 case of hemiplegia in a man who had secured symptomatic relief and stopped the treatment.

Our best results are obtained in those patients who show: 1, not too much change in arterioles and capillaries; 2, a low natural blood

sulfocyanate concentration; 3, satisfactory response to small doses of sulfocyanates; 4, a blood concentration of 2.5 to 5 mg. of sulfocyanate per 100 cc. of blood while on treatment; 5, full coöperation in the treatment.

TABLE 1.—RESULTS WITH POTASSIUM SULFOCYANATE

No. cases	Age group	Race		Sex		Results			Type of hypertension			Classification of patients*	
		W.	C.	M.	F.	Good	Fair	Poor	Essential	Luetic	Decompensation		
22	20-40	15	7	10	12	14	2	6	19	2	1	A-1 B-5	C-10 D-6
71	40-60	54	17	41	30	47	8	16	64	3	4	A-8 B-11	C-17 D-35
43	60-80	39	4	27	16	31	6	6	34	4	5	A-11 B-5	C-11 D-16
136		108	28	78	58	92	16	28	117	9	10		
Per cent:						67.7	11.7	20.6					

Classification of results:

Good: Above 15% reduction in systolic and diastolic pressure.

Fair: Above 10% reduction in systolic and diastolic pressure.

Poor: Below 10% reduction in systolic and diastolic pressure.

* A—North Carolina State Hospital. B—North Carolina State Prison. C—Rex Hospital Clinic. D—Private patients.

Conclusions. 1. Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance. The concentration is approximately 50,000 times that of nitrites.

2. Each individual has a fixed constant blood sulfocyanate level.

3. Blood sulfocyanate concentrations tend to vary inversely with the blood pressure level, whether naturally or under treatment.

4. There appears to be normally in the body a balance between pressor substances and sulfocyanates. There is a definite tendency for low blood sulfocyanate levels to be associated with hypertension. Higher concentrations of blood sulfocyanates are not associated with hypertension.

5. Potassium sulfocyanate is a safe depressor substance if used properly; it lowers the diastolic pressure as well as the systolic.

6. The earlier in the course of the disease that treatment is instituted, the better the results that can be anticipated.

7. The lower the effective blood sulfocyanate concentration can be kept during treatment, the better the results will be.

8. The results of this work show such a strong rationale for the use of sulfocyanates in hypertension that the use need no longer be regarded as empirical.

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THE EFFECT OF POTASSIUM THIOCYANATE ON THE OCCURRENCE OF MIGRAINE

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A STUDY of the effect of thiocyanate on the occurrence of migraine headaches seemed of interest for two reasons: The first of these is the more recent understanding of the local mechanism responsible for the signs and symptoms of migraine, with emphasis on the supposition that all attacks of migraine begin with an excessive vasoconstriction of certain branches of the carotid artery. If this supposition be true, there would seem to be a possibility of preventing the attacks by the use of a long-acting vasodilator substance, such as potassium thiocyanate seems to be. The second reason for this study is the desirability of improving our present methods of treatment of migraine. There is no intention to review here such methods of treatment. The reader is referred to an excellent review of this subject by von Storch,⁹ which is summarized in part as follows: "Therapeutic results are still far from satisfactory in migraine. Termination of individual attacks can be accomplished in most instances. The frequency and severity of attacks may be decreased in many cases. Complete relief is unusual." A more effective means of preventing migraine attacks would indeed be of considerable clinical value.

Although the apparent nature of the migraine mechanism has been long suspected on the basis of certain clinical observations, we are indebted to Wolff and his collaborators^{5,8} for convincing experimental evidence on this subject. By means of special methods they were able to observe the caliber and pulsations of the temporal and middle meningeal arteries in relation to attacks of migraine. They found that the pain of migraine was associated with an increase in the amplitude of pulsations and the caliber of the

arteries. The relief from pain which followed the administration of ergotamine tartrate coincided with a diminution in the arterial pulsations and diameter; on the other hand, the increase in pain which followed injections of histamine was associated with an increase in the caliber and pulsations of the arteries. Thus, these and other observations by the same group of investigators constitute evidence that the pain of migraine is due to an excessive distention of extracranial and dural branches of the carotid artery.

These observations on the mechanism of pain in migraine may be less important clinically than a study of the vasomotor reactions associated with the pre-headache phenomena of this disorder. Of considerable significance may be the demonstration by Schumacher and Wolff⁸ that under certain conditions the pre-headache scotomata of migraine could be abolished by the administration of the vasodilator substance amyl nitrite. From this observation one may infer that the initial vasomotor reaction, which occurs during the pre-headache phase of migraine, is one of excessive vasoconstriction of intracerebral vessels. In addition, it seems possible that initial vasoconstrictor reactions are not confined to intracerebral vessels, but involve the dural and extracranial vessels as well. It was on the basis of such a possibility that this study has been made—that is, to determine the effect of the vasodilator substance potassium thiocyanate on the frequency and severity of migraine.

Potassium thiocyanate was the chosen vasodilator drug for several reasons. It has been found to exert a prolonged depressor effect on the blood pressure of hypertensive patients in about half of the cases in which it has been employed.¹ This effect is seemingly due to peripheral vasodilatation because, first, the decrease in blood pressure occurs before any change in the composition of the blood,⁷ and second, its effect on the blood pressure is enhanced following bilateral splanchnic and lumbar sympathectomy.⁴ Furthermore, in our experience when potassium thiocyanate has been effective in reducing the blood pressure of a hypertensive individual, there has also been a definite decrease in the patient's response to the cold-pressor test. We regard this as evidence that potassium thiocyanate not only produces a mild peripheral vasodilatation in these cases, but in addition restrains the peripheral vasoconstrictor responses to stimuli of cold and pain. Since the advent of a method for the proper control of thiocyanate medication, as published by Barker in 1936,² it has been possible to give the drug intelligently with a minimum of risk. Recently Barker¹ and Kurtz⁶ have separately reported their observations on the use of thiocyanate covering periods of 10 and 11 years, respectively. In their hands, serious reactions have been rare and fatalities charged to the drug have not occurred. However, other authors have attributed fatalities to the drug, even when given under controlled conditions. Attention

has been called to these reports by "Current Comment" in *The Journal of the American Medical Association*.³ It is indisputable that the drug is potentially dangerous and should not be used without the necessary measures to control its blood concentration.

Material. The observations in this report were begun in November, 1940 (15 months ago) and are based on a study of 13 patients with migraine who have received potassium thiocyanate. The average period of observation for each patient has been 11 months. Patients who have been started on treatment less than 6 months ago have not been included in this report. Case histories have been kept as completely as possible, and, before compiling this report, answers to a detailed questionnaire were obtained from all patients included in this study.

The diagnosis of migraine was based on the following clinical considerations: All patients had been subject to attacks of severe headache with periods of complete freedom between attacks. In 11 of the 13 patients these attacks had been present since childhood or early adult life. A family history of "sick headache" was obtained in 11. In 10 patients the pain had been hemicranic. The pain, when severe, was of a throbbing character in 6. Nausea, with or without vomiting, was associated with the attacks of 10. In 2 patients manual compression of the carotid artery on the side corresponding to the pain brought temporary relief. In 10 women the attacks regularly occurred in close association with the menstrual flow.

Method. Two separate procedures were followed, depending upon the frequency of the migraine attacks experienced by the individual to be treated. First, patients who had been having migraine attacks as frequently as 3 times per month, or who had coexisting hypertension, were instructed to take daily dosages of thiocyanate in the amounts of 6 gr. daily for 3 days, and then 3 gr. daily. After about 10 days the blood thiocyanate concentration was determined by the method of Barker.² No attempt was made to prescribe dosages of the drug that would produce optimum blood concentration of 8 to 12 mg. per 100 cc. as suggested by Barker for the treatment of hypertension. On the contrary, dosages were prescribed that would produce the lowest blood concentration effective against migraine.

Second, patients who had migraine attacks less frequently than 3 times per month and who could foretell the onset of an attack were advised to take 6 gr. of potassium thiocyanate when an attack seemed imminent. Because the drug was dispensed in enteric coated tablets,* patients were directed to crush the tablet in the mouth before swallowing. Four of the 13 patients were treated in this manner.

Patients whose attacks of migraine occurred less frequently than 3 times per month were not included in this study unless they could foretell the onset of attacks or had a coexisting hypertensive disease.

Results. To facilitate description of results, we shall use the terms "mild headache" and "severe headache," with arbitrarily assigned definitions for each of these terms. "Mild headache" refers to a headache of mild discomfort and of less than 4 hours' duration. "Severe headache" designates a headache of greater severity and of longer duration. It will be appreciated that a "mild headache" is of minor consequence to the real migraine

* We are indebted to Eli Lilly Company for "Enseals" Potassium Thiocyanate used in this study.

sufferer. However, in the discussion that follows we shall include the mild headaches to describe the results more accurately.

Twelve of the 13 patients received substantial relief from migraine while taking thiocyanate. Of these 12, 4 patients obtained complete relief from headache of any description; 7 patients, who were relieved of severe attacks, experienced mild headaches with a frequency ranging individually from 1 to 8 times per month; 1 patient with an associated severe hypertension experienced an occasional severe migraine attack premenstrually. Only 1 of the 13 patients received no benefit from thiocyanate. In addition to migraine this patient suffered from severe allergic manifestations. She received daily dosages of potassium thiocyanate for 3 months with the blood thiocyanate concentration reaching 4.4 mg. per 100 cc.

TABLE 1.—EFFECT OF THIOCYANATE ON THE OCCURRENCE OF MIGRAINE

Case	Average frequency of migraine headaches per month				Daily dosage, gr.	Blood concentra- tion, mg.	Period of observation, mos.
	Before thiocyanate therapy		During thiocyanate therapy				
	"Mild"	"Severe"	"Mild"	"Severe"			
1*	0	2	0	0-1	4	7.5	15
2	0	12	0	0	3	2.3	15
3*	15	1-2	4	0	3	6.6	13
4*	8-12	0-1	0	0	6	6.2	12
5	0	6	1	0	3	...	2†
6	18	12	8	0	3	2.5	11
7	3-4	1-3	3-4	1-3	6	4.4	3†
8	22	8	4	0	6-9	4.5-8.3	8
9	0	10	0	0	3	3.4	7

* Migraine associated with hypertensive disease. See text.

† Discontinued thiocyanate therapy. See text.

In Table 1 is assembled data listing the approximate frequency and severity of headaches before and during thiocyanate treatment, the daily dosages employed, and the blood thiocyanate levels for individual patients who have taken daily dosages of the drug. It is noteworthy that 5 of 8 patients who were benefited required only 3 gr. of thiocyanate daily to obtain a satisfactory effect. The blood thiocyanate levels for these 5 patients ranged from 2.4 to 6.6 mg. per 100 cc. It is apparent that the blood levels of thiocyanate effective against migraine are substantially lower than those generally considered to be most effective in the treatment of hypertension. Three patients in the group had a coexisting hypertension, which in no way seemed to alter the result of treatment.

An observation of considerable significance was afforded by the fact that 5 patients who had obtained relief from migraine while taking thiocyanate voluntarily discontinued the medication. In the case of 1 patient, severe headaches recurred only preceding the menstrual periods. The other 4 patients experienced a recurrence of headaches of approximately the same frequency and severity as obtained before treatment was begun. In each case the resump-

tion of thiocyanate medication again brought relief from the migraine attacks.

Case Report. The following case history is included because the extreme severity of the migraine experienced by this patient provided an excellent object for study.

A white male executive, age 45, had been subject to frequent "sick headaches" as long as he could remember. For several years he had had a mild attack daily, and severe attacks on the average of twice each week. During the latter he frequently had to be driven home from work and put to bed. In preceding years he had employed many forms of treatment, including large dosages of sedatives and vitamin B-complex, without relief. Sole relief was obtained from ergotamine tartrate taken at the onset of an attack. However, attacks thus aborted were prone to recur within a few hours, and at times he had taken 4 dosages of ergotamine tartrate daily. On the advice of his family physician this medication was discontinued.

When he presented himself for examination in June, 1941 (8 months ago) he was developing a right hemicranic headache. Pressure on the right carotid artery relieved pain. On the preceding day he had experienced a moderately severe left hemicranic headache, which possibly accounted for the well-developed periarteriolar sheathing observed in the fundus of the left eye. This finding was not present at a later examination. The right fundus appeared normal. The blood pressure was within normal limits, and the remainder of the physical examination revealed no important abnormality.

Thiocyanate medication was begun, and at the end of 2 weeks the blood thiocyanate level measured 6 mg. per 100 cc. The patient stated that contrary to instructions he had taken 6 gr. of thiocyanate daily. During this period he had had only 3 moderately severe headaches and on the remaining days had had no headaches at all so that he was much encouraged. During the next 6 weeks the patient took 9 gr. of thiocyanate daily, which resulted in an elevation of the blood thiocyanate concentration to 8.3 mg. per 100 cc. During this period he experienced an average of 1 to 2 mild headaches weekly. There had been 1 severe headache. He estimated the degree of relief as about 90%.

After continuing this program for about 2 months, the patient voluntarily discontinued the medication for 2 weeks, during which there was a recurrence of frequent violent headaches. During the next 2 weeks he endeavored without success to obtain relief by taking 6 gr. of thiocyanate at the very onset of the headaches. Whereupon, a daily dosage of 6 gr. of thiocyanate was resumed. Two months later the blood thiocyanate measured 4 mg. per 100 cc., and the patient reported that he had been having an average of 1 mild headache weekly. Violent headaches had not occurred.

The results obtained by the second group of patients—those who have taken thiocyanate only when a migraine attack seemed imminent—can be described briefly. One patient, who had been subject to a severe attack of migraine preceding each menstrual period for years, has over a period of 10 months been able to prevent the occurrence of headaches by taking 6 gr. of thiocyanate daily for 2 or 3 days preceding the menses. There were 2 women who had each been subject to an average of 2 severe attacks of migraine monthly. One of these has been able over a period of 6 months to prevent the headaches by taking 6 gr. of thiocyanate at the

onset of pre-headache symptoms consisting of "extreme tension." The other patient was able to prevent the headaches from becoming severe by taking 6 gr. of thiocyanate at the very onset of the attack. However, this patient discontinued this procedure after 2 months because of untoward symptoms consisting of "uneasiness around the heart" and "pain in my hemorrhoids and varicose veins." The fourth patient in this group, a salesman, age 35, had experienced severe headaches on an average of 2 a month and milder headaches about 3 times monthly for several years. Over a period of 11 months he has been able to prevent the occurrence of headaches by taking 6 gr. of thiocyanate at the onset of prodromal symptoms, which, he declared, are too vague to be described.

Several patients have experimented with taking thiocyanate after the onset of headache. In all instances thiocyanate taken in this way has failed to bring relief. It must, therefore, be emphasized that for thiocyanate to be effective in preventing attacks of migraine it must be taken in daily dosages or taken during the pre-headache phase of the attack.

Comment. The observations herein reported indicate that potassium thiocyanate, properly administered, is effective in reducing the frequency and severity of migraine headaches.

The success of thiocyanate in reducing the frequency and severity of attacks of migraine is, in the light of present knowledge of the drug, probably due to its prolonged vasodilator action. Should this supposition be true, it would constitute additional evidence that the initial vasomotor reaction in migraine is one of excessive vasoconstriction of the involved branches of the carotid artery, and it would establish the logic of employing long-acting vasodilator drugs in the treatment of migraine. However, it is possible that the effectiveness of thiocyanate in the treatment of migraine depends upon some unknown action of the drug—a consideration which emphasizes the speculative nature of the above reasoning.

The clinical value of potassium thiocyanate in the treatment of migraine cannot at present be fully determined. The excellent results observed in this study would seem to justify its trial in the following groups of patients; first, those patients who by their ability to foretell the onset of attacks can obtain a satisfactory result with the use of small quantities of the drug; second, those who suffer a degree of morbidity from migraine sufficient to justify the daily administration of the drug; and lastly, those migraine sufferers who have an associated hypertensive disease.

However, a decision to employ thiocyanate in the treatment of migraine must take into consideration the potential toxic properties of the drug. The effects of overdosage with thiocyanate have been clearly described^{1,7} and can be prevented by the use of certain safeguards in the administration of the drug. But even so, there is still the question of possible harmful effects from the prolonged

administration of the drug. It is encouraging that the experiences of others,^{2,4} who have employed the drug in the treatment of hypertension for more than a decade, have not furnished evidence of ultimate deleterious effects from the prolonged intelligent administration of the drug. However, it is recognized that a longer period of observation will be necessary before reaching a final conclusion on this very important question.

Summary. Potassium thiocyanate in daily dosages sufficient to produce a blood concentration of the drug of 2.5 to 8 mg. per 100 cc. is effective in reducing the frequency and severity of migraine headaches. Potassium thiocyanate in 6 gr. dosages taken during the pre-headache phase of a migraine attack is useful in aborting the headache. On the other hand, potassium thiocyanate taken after the onset of actual headache is of no value.

The rationale of treating migraine with the use of long-acting vasodilator drugs is discussed. The possibility of harm resulting from overdosage or long-continued administration of a potentially dangerous drug, such as potassium thiocyanate, in the treatment of migraine, has not been entirely eliminated, though positive evidence is still lacking.

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THE LOCALIZING VALUE OF THE CLINICAL, ELECTROENCEPHALOGRAPHIC, AND PNEUMOENCEPHALOGRAPHIC FINDINGS IN EPILEPSY

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It is the purpose of this paper to compare the relative values of the clinical study, the electroencephalogram (E.E.G.), and the pneumoencephalogram (P.E.G.) for the localization of focal cerebral lesions in convulsive disorders. The electrical seizure patterns in cases of symptomatic epilepsy will be compared with those in patients with idiopathic epilepsy, and the effects of hyperventilation upon

the inducement of these waves noted. The variations in the alpha, beta, and delta waves, also the pneumoencephalographic abnormalities present will be described; also our findings as to the correlation of these abnormalities with any significant changes in the E.E.G.

Studies upon the comparison of the clinical signs, E.E.G. and P.E.G. observations have been made by Yeager *et al.*,⁴⁵ Davidoff,⁸ Rheinberger and Siris,³⁶ Goldensohn, Marmor and Meyer.²²

In this series of 52 cases, 24 (46.2%) were classified as idiopathic epilepsy. Of these 24, there were 18 (75%) with seizure patterns. These 18 cases consisted of 6 instances of grand mal, 6 petit mal, and 11 of psychomotor epilepsy. Four patients had a combination of 2 or more seizure patterns, hence are listed twice in the preceding classification.

Twenty-eight patients (53.8%) of the entire series had symptomatic epilepsy. The symptomatic group was classified as follows: traumatic in 8 (15.2%); brain tumor in 5 (9.6%); mental deficiency, dating from birth and of undetermined origin in 6 (11.5%); vascular lesions in 4 (7.7%); congenital communicating hydrocephalus in 3 (5.8%); encephalitis in 1 (1.9%); and por-encephalus in 1 (1.9%).

In this symptomatic group there were 14 (50%), who had seizure patterns. These seizure patterns consisted of 7 grand mal, 2 petit mal, and 8 psychomotor. In 2 patients there were 2 or more of these seizure patterns present. It thus may be noted that the occurrence of seizure patterns in the symptomatic epilepsy group was 21.2% less than in the idiopathic group.

In the entire group of 52 patients there were 32 patients (61.5%) in whom E.E.G. seizure patterns were present; whereas in 20 (38.5%) they were absent. In 6 cases, 2 or more types of seizure patterns existed. Grand mal patterns were found in 13 instances (23.4%); psychomotor waves in 19 patients (36.5%); petit mal in 7 (13.4%); and 6-cycle waves in 4 cases (7.7%).

In order to verify the existence of epilepsy during the latent period, artificial means of precipitating these convulsive patterns, or even of bringing on the convulsions, should be utilized. Hyperventilation is the most simple of these methods. In this series 16 were hyperventilated, and in 12 (75%) specific seizure patterns were so induced. These seizure patterns were: grand mal 3, petit mal 3, psychomotor 5, and combinations of these in 1.

In addition to the specific epileptic patterns present in the E.E.G., there were certain other abnormalities. Increased beta voltage was present in 13 cases (25%), 16 cases (30.8%) showed unequal alpha, 31 patients (59.6%) had delta patterns, and 12 cases disclosed increased beta voltage combined with delta pattern. In only 2 instances was the E.E.G. entirely normal; both cases were traumatic.^{15,16,17,29}

When unilateral lesions did not involve the occipital lobe, it has been reported that the affected side showed a much stronger alpha rhythm (Lemere).²⁸ In our series, 16 patients showed differences in the alpha between the two occipital areas. In 8 of them the strongest alpha was on the side of the lesion, and in an equal number it was on the other side. In none of these cases was a lesion of the occipital lobe indicated.

In 33 patients delta and seizure waves originated in a circumscribed area of the brain. Such an E.E.G. is defined as a focal E.E.G. In 6 cases there were 2 or more foci in widely separated regions of the brain that gave rise to delta and seizure pattern, and these were termed cases of multiple foci. There were 11 patients in which the delta and seizure waves alternated with normal wave patterns in all areas in the brain. This type was called "diffuse foci."

In 8 instances, 15.4%, a normal P.E.G. was found, while in 44 (84.6%) some abnormality was noted. These abnormalities were noted. These abnormalities consisted of unequal ventricles in 35 patients (67.3%), decreased cortical air in 18 patients (34.6%), hydrocephalus in 11 (20.4%), increased cortical air in 11 (20.4%), ventricular shift in 9 (17.3%), subdural air in 2 (3.8%), dilated third ventricle in 2 (3.8%), and a very small ventricle in 1 patient (1.9%).

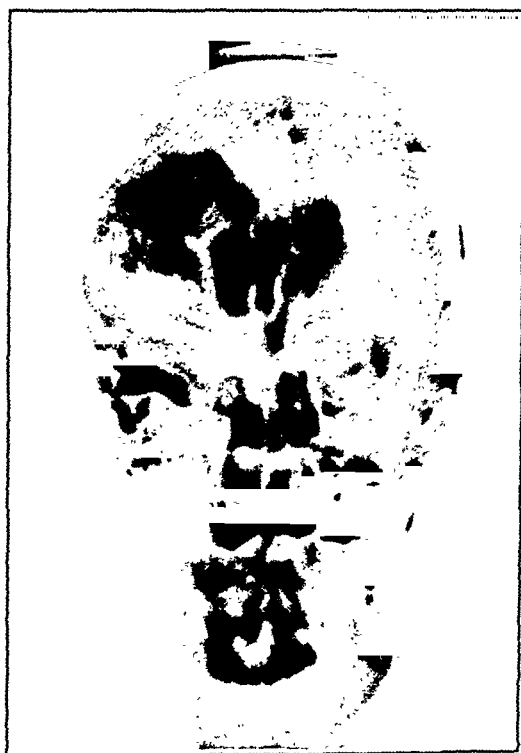
In those patients with unequal ventricles the E.E.G. did not demonstrate any consistent pattern. In those cases in which there was decreased cortical air, there was no pattern diagnostic of such a change upon E.E.G. examination.

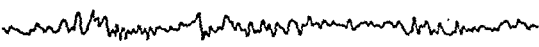
Increased cortical air markings interpreted as atrophy occurred in 11 instances (20.4%). Rubin³⁸ found it was possible to localize atrophy of the cerebral cortex in schizophrenic patients by comparing the alpha rhythms of the various regions of the two hemispheres with each other. His findings were confirmed by P.E.G. in 8 out of 9 patients. Our study did not verify Rubin's observations.

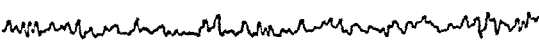
Ventricular shift was present in each of 9 patients (17.3%). Ventricular shift is caused by mass-displacing lesions, such as tumor, abscess or hemorrhage; by cerebral atrophy or cerebral cicatrix. In the mass-displacing lesions the shift is to the opposite side of the lesion, whereas in atrophy or adhesions there is a shift to the side of the lesion.^{4,5,14,37} In 5 of these cases there was a mass-displacing lesion, and in 4 of them atrophy and cerebral cicatrix was present. In all 9 the E.E.G. accurately localized the side of the lesion.

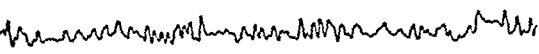
Hydrocephalus may be of a communicative or obstructive type. Obstructions may exist in the third ventricle, aqueduct, or subarachnoid channels. In this group there were 11 cases with hydrocephalus, 3 being of the congenital communicating type. In only

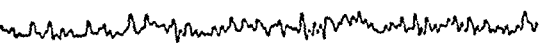
1 case was a focal lesion demonstrated both by clinical and E.E.G. observation. In none of these was a focal lesion demonstrated by the air studies. Two of this group showed unequal ventricles. The E.E.G. demonstrated grand mal attacks in 2 instances, psycho-



L.F. 

L.P. 

L.O. 

R.O. 

R.P. 

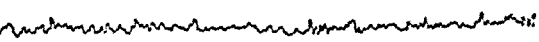
R.F. 

FIG. 1.—Case A. S. Porencephalic cyst with generalized epilepsy. The E.E.G. (electroencephalogram) shows grand mal waves in the left occipital and parietal region with irregular alpha on the right side. The P.E.G. (pneumoencephalogram) shows a porencephalic cyst in the right frontal region.

motor in 1, irregular alpha in 1, increased beta in 1, and diffuse abnormalities in 2. In the entire group of 11 cases, 4 demonstrated a superimposed beta on the delta with an increased beta voltage. This was also present in the 1 case of porencephalus (Fig. 1).

In the series, the E.E.G. localized lesions in 33 cases (63.3%), the clinical findings in 31 (59.3%), and the air studies in 9 cases (17.2%).

Localized abnormalities of the E.E.G. occurred in the prefrontal and premotor areas in 10 patients; motor area, 5; parietal-temporal, 5; occipital, 5; suprasellar, 3. Clinical signs localized lesions in the prefrontal and premotor areas in 2 cases, motor area in 26, suprasellar in 3. The P.E.G. localized lesions in the prefrontal and premotor areas in 2 instances; motor area, 3; suprasellar, 3; occipital, 1. It is quite apparent that in cases of convulsive disorders lesions are not found as frequently in the parietal-temporal and occipital areas as they are in the frontal lobe.

In this entire series of cases there were 31 patients (59.6%) who had clinical focal epilepsy, and 21 patients (40.4%) who had clinical non-focal epilepsy.¹²

In 10 of the 31 cases of clinical focal epilepsy, the E.E.G. and the clinical signs localized the lesion in the same lobe. In 7 of the 10 cases the P.E.G. also localized the lesions in the same lobe. In 9 patients the clinical findings and the E.E.G. localized the lesion on the same side, but the E.E.G. did not coincide with the clinical signs as to lobe involvement. In 2 of these 9 cases the P.E.G. and the clinical signs accurately localized the lesion, but the E.E.G. failed to do so. In 3 patients the clinical findings and the E.E.G. findings localized the lesions in entirely different places. In 7 instances in which the clinical signs definitely localized a single lesion, the E.E.G. showed abnormal electrical activity throughout the brain. In 1 case wherein the clinical signs definitely localized the lesion, the E.E.G. showed 2 separate areas of abnormal electrical activity, and in 1 case the clinical signs localized a lesion while the E.E.G. was normal.

In the 21 cases in which the clinical signs showed no evidence of focal epilepsy, the P.E.G. also failed to demonstrate a focal lesion. The E.E.G., however, showed 13 cases in which the area of abnormal electrical activity was confined to one lobe; 3 instances of multiple foci, and 4 instances of the diffuse type. There was only 1 patient who had an entirely normal E.E.G.

The E.E.G. was a definite aid in the localization of cerebral dysfunction. When the clinical findings and the air studies failed to demonstrate the area of abnormality within the brain substance, the E.E.G. frequently gave us evidence as to the location of the affected area.

Without the use of the P.E.G. many cases of convulsive seizures would be classified as idiopathic epilepsy because the exact intra-

cranial pathology is not apparent upon clinical study. The P.E.G. aids in segregating such cases as tumors, traumatic or porencephalic cysts, cerebral atrophies and cicatrix, and obstructive and communicating hydrocephalus of varying grades.^{20,21,42}

In 24 patients of idiopathic epilepsy, the P.E.G. revealed 16 with unequal ventricles, 4 slight hydrocephalus, 5 decreased cortical air, 5 increased cortical air, 1 case of subdural air, and 4 normals. The abnormalities found in idiopathic epilepsy have been reported by others.^{2,7,10,13,23,25,26,30,31,43}

The E.E.G. showed 6 patients with grand mal, 5 petit mal, 11 psychomotor, 8 unequal alpha, 3 increased beta, and 3 diffuse delta. None of these patients had normal E.E.G. Thirteen patients (42%) demonstrated focal abnormalities by clinical signs, while the P.E.G. failed to localize any specific lesion.

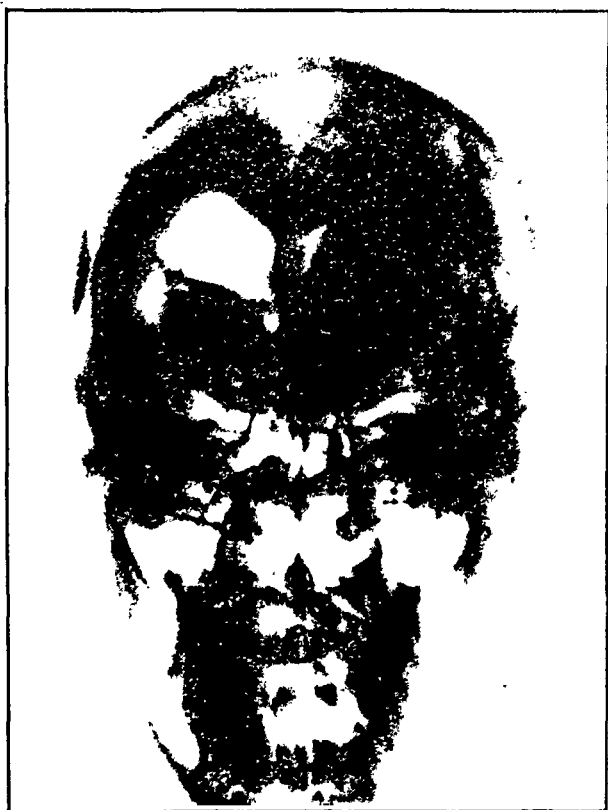
Traumatic epilepsy may be focal or generalized. In cases of depressed fracture or gunshot wounds a local area of the brain is destroyed and there is a tendency toward focal convulsions (Glaser and Shafer).¹⁸ The percentage of patients with generalized convulsions associated with cerebral concussion and trauma is low (1.8%) (Glaser and Shafer).¹⁹ Trauma may produce generalized hydrocephalus, localized areas of cortical atrophy, or meningocerebral cicatrix (Foerster and Penfield),¹⁴ with migration of the ventricles toward the lesion and traumatic cysts.


There were 8 cases of traumatic epilepsy in this series (Fig. 2). In 6 cases (88%) both the E.E.G. and the clinical findings accurately localized the lesions. In 3 of these the P.E.G. confirmed the diagnosis. The P.E.G. abnormalities consisted of 7 instances of unequal ventricles, with 3 of these 7 having a shift to the side of the lesion, 3 air, 1 subdural air and 1 traumatic cyst.³⁴ The P.E.G. was abnormal in all 3 patients, with traumatic epilepsy. The E.E.G. examination indicated 2 cases of grand mal, 1 psychomotor, 5 unequal alpha, 2 increased beta, and 2 normal. These 2 patients were the only ones with normal E.E.G. in the entire series.

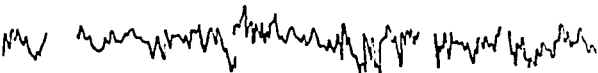
Convulsive seizures are frequently associated with brain tumor. Sargent,⁴⁰ in 240 cases, reported 30% of the patients with brain tumors developed epilepsy, while Parker³² in 313 cases reported 21.6% developed epilepsy. Penfield, Erickson and Tarlov,³³ in 703 cases of brain tumor, reported that the occurrence of convulsive seizures depended upon the location of the tumor as well as the pathology. Convulsive seizures were found in 37% of all intracranial tumors and 45% of all supratentorial tumors. Dowman and Smith⁹ reported 39% had convulsions, of which 21% were focal in character. Sachs and Furlow³⁹ found 34% of the patients with tumors developed convulsions, while Peterman³⁵ reported 29% developed convulsions.

The accuracy of the E.E.G. in localization of brain tumors has been reported by Jasper²⁴ to be in the neighborhood of 90% to 95%;

Baldes *et al.*¹ reported 86% accuracy. The localization of cerebellar, suprasellar and other subcortical lesions by the E.E.G. is still in the experimental stage.^{41,44}



R.O. 

R.P. 


R.F. 

FIG. 2.—Case E. R. Depressed skull fracture over the right motor area with right hemiparesis. The epileptic seizures were generalized, but the E.E.G. demonstrated grand mal waves originating from the left motor area, thus coinciding with the clinical localization. The P.E.G. demonstrated a dilated left lateral ventricle with a shift to the left.

The E.E.G. in this series of 5 cases of brain tumor showed psychomotor waves in 1 case, irregular alpha in 1, increased beta in 2, diffuse abnormalities in 2 (Figs. 3 and 4). The air studies indicated

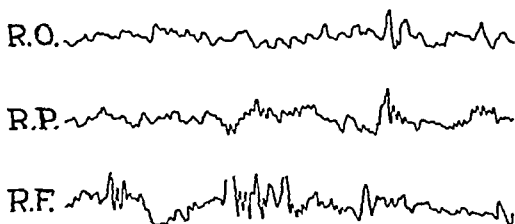
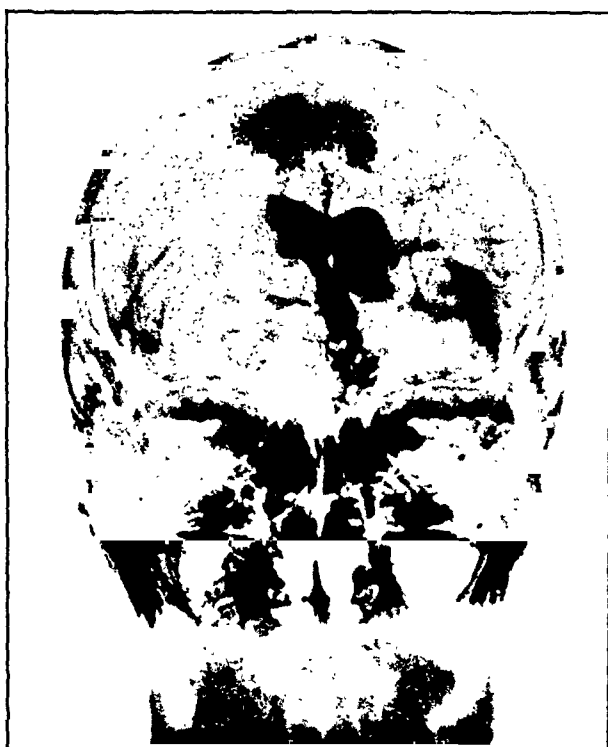
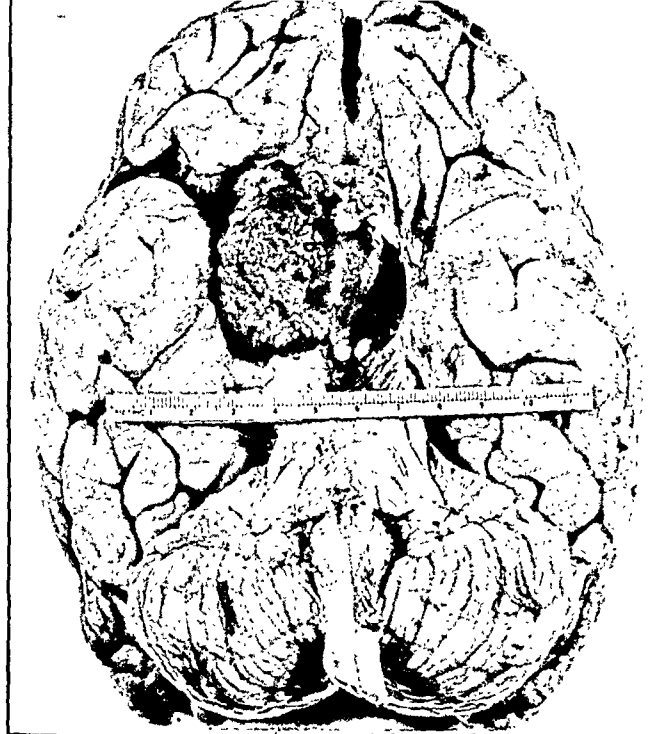


FIG. 3.—Case M. B. Meningioma situated in the right motor area directly in mid-line with focal epileptic seizures. The E.E.G. and the P.E.G. all localized the lesion accurately.

LEGEND FOR FIG. 4.

FIG. 4.—Case I. R. The patient had a large sphenoidal ridge meningioma situated on the right side, the epileptic seizures were focal in character. The E.E.G. localized a deep-seated lesion in the right frontal area. The P.E.G. also indicated a deep-seated lesion situated over the right base.



R.F. ~~~~~

R.P. ~~~~~

R.O. ~~~~~

FIG. 4.—(For legend see opposite page.)

unequal ventricles in 3 cases, decreased cortical air in 3, hydrocephalus in 1, and a normal P.E.G. in 1. This last patient had a pituitary tumor. Focal lesions were demonstrated by clinical and electrical studies in 5 patients, while the air studies localized the lesions in 4 of them.

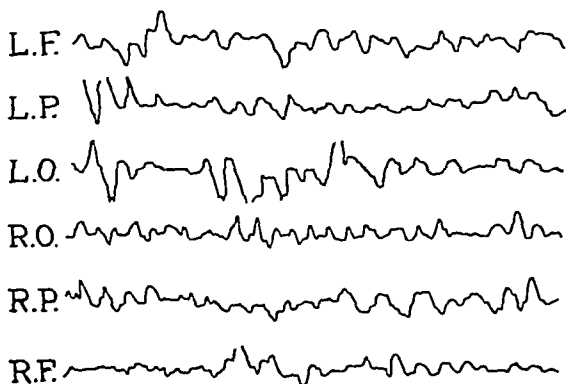
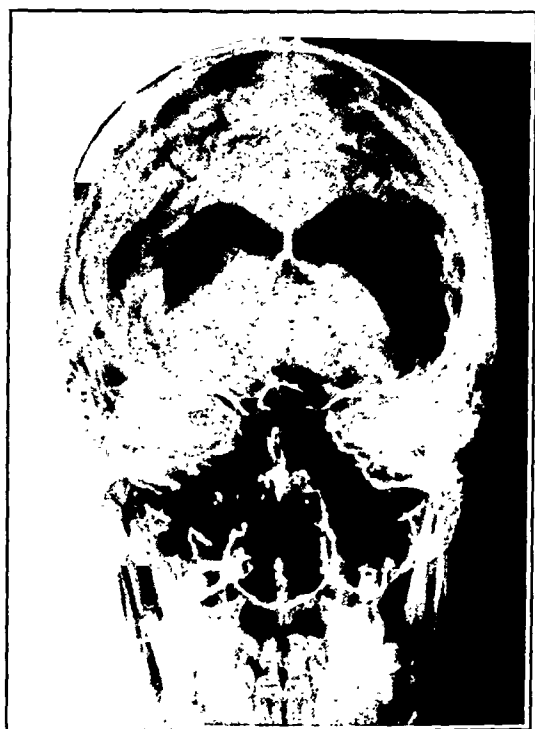


FIG. 5.—Case H. G. Dilatation of the ventricles (left side larger), with atrophy due to a vascular lesion. Focal convulsions (left). The E.E.G. shows grand mal and psychomotor waves over the entire left hemisphere. This coincided to a certain degree with the air studies, which indicated that the left lateral ventricle was larger than the right. It is interesting to note that the patient had left-sided focal attacks.

There is a group of children and infants with mental and physical retardation whose nervous system shows evidence of cerebral damage, which presumably dates from birth. The exact etiology of such conditions is difficult to ascertain, but they may be due to some vague intra-uterine condition, to degenerative diseases, developmental defects, anoxemia, or other causes of uncertain origin.

The conventional diagnosis of feeble-mindedness, or cerebral palsy, does not define the anatomical defect, or the physiologic residue. The P.E.G. may be entirely normal, or demonstrate certain anatomic changes within the brain. These abnormalities consist of variations in the size and shape of the ventricles, and the subarachnoid space. The dilatation of the ventricles in these cases is rarely due to obstruction, but is usually caused by atrophy with a compensatory enlargement.^{3,6,11,27}

Six mentally defective children had focal lesions demonstrable by the E.E.G. in 5, by clinical signs in 4, and in none of them by the air studies. The P.E.G. findings consisted of 4 cases of unequal ventricles, 1 with slightly dilated ventricles, 2 with decreased cortical air, 1 with increased cortical air and 1 normal. E.E.G. findings were abnormal in all 6 cases. The abnormalities were petit mal 1, psychomotor 3, unequal alpha 1, and diffuse delta in 1.

Cerebrovascular lesions consisting of thrombosis or embolus may cause a local atrophy with the resulting dilatation and migration of the ventricles, cysts, dilatation of both ventricles and cortical atrophy. In some instances the ventricular system may be entirely normal. In the 4 cases of this series, 2 patients had unequal ventricles, as well as increased cortical air. The other 2 patients had entirely normal P.E.G. The E.E.G. revealed 1 case of grand mal, 2 cases of psychomotor patterns, and 3 instances of diffuse delta activity. In 3 instances the clinical signs demonstrated focal lesions, while the E.E.G. and the P.E.G. only demonstrated a focal lesion in 1 case (Fig. 5).

Summary. 1. The electroencephalogram (E.E.G.) pointed to focal epilepsy in 33 of our 52 cases (63.3%); the clinical findings in 31 (59.6%); and the air studies in 9 (17.2%).

2. The pneumoencephalogram (P.E.G.) was normal in 8 cases (15.4%) and the E.E.G. was normal in 2 cases (3.8%).

3. Of 32 patients, 61.5% had seizure patterns upon electroencephalographic examination. We would expect a greater number of seizure patterns if it had been possible to hyperventilate each case.

4. Of the 52 cases, 24 (46.2%) were classified as idiopathic epilepsy, of which 18 (75%) had seizure patterns; 28 (53.8%) had symptomatic epilepsy of which 14 (50%) had seizure patterns.

5. Delta patterns were present in 31 (59.8%); unequal alpha in 16 (30.8%); increased beta voltage in 12 (23.5%).

6. From a clinical standpoint, 31 patients (59.6%) had focal epilepsy, and 21 patients (40.4%) had generalized epilepsy.

7. The E.E.G. demonstrated areas of abnormal activity in 30 of the 31 cases of focal epilepsy, and 20 of the 21 cases of non-focal epilepsy. In those with non-focal epilepsy, the E.E.G. was the only evidence that areas of abnormal activity existed in the brain.

8. In the cases of this series the abnormalities, as indicated by the three tests, were more frequently located in the frontal lobes.

9. Patients with either idiopathic or symptomatic epilepsy presented the same types of clinical convulsions and the same types of electrical seizure patterns; and hyperventilation induced all types of seizure patterns.

10. The P.E.G. demonstrated ventricular shifts in 9 cases. The E.E.G. localized the side of the lesion in each instance. Specific electroencephalographic abnormalities were not found in patients with increased or decreased cortical air or unequal ventricles. Severe hydrocephalus showed increased beta voltage combined with delta.

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THE EFFECT OF SULFONAMIDES UPON ARTIFICIAL FEVER PRODUCED BY PEPTONE IN ANIMALS*

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THE investigation reported here represents a delayed study of a clinical antipyretic action noted in the late spring of 1936 with two sulfonamides, "P.T. 353," and "P.S. 364" later called Prontosil and Prontosil-Soluble, provided through the courtesy of Professor H. Hörlein in May, 1936. The fall in febrile body temperatures seen in those early days suggested that these drugs might be acting upon the hypothalamic temperature centers. Substantiating this suggestion were the early toxicologic studies of Halpern and Mayer,¹ which indicated that large doses of sulfonamides (sulfanilamide) had a subcortical site of action in the central nervous system. A marked fall in the normal body temperature of mice, rats, guinea pigs, rabbits and cats has been reported with large, lethal or sublethal doses of sulfonamides by several authors.² In all of these animal experiments, the dose of sulfonamides employed was a very large one, being many times the maximal therapeutic dose per unit body weight as used in human therapeutics, and it is quite possible that the lowering of body temperature was part of a shock syndrome which may accompany the administration of excessive amounts of many drugs.

* This paper was presented at the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics, Boston, April, 1942.

There is abundant evidence that sulfonamides reduce febrile temperatures in animals or patients host to those infections toward which the sulfonamides are specific chemotherapeutic agents. There is little experimental evidence to indicate whether these drugs in therapeutic doses act upon the temperature-controlling mechanism of the body *per se* or upon the pathogen producing the fever. Beeson and Janeway³ gave various sulfonamides to rabbits in doses which were not stated in relation to body weight but which would probably correspond to about 0.5 gm. per kilogram by mouth and they got little effect upon normal body temperature or upon artificial fever produced by typhoid vaccine. The drugs were also injected intravenously and then it was found that sulfapyridine had an antipyretic action in rabbits. The number of animals used was not stated.

Method. Experiments will be described in which various sulfonamides were given by mouth (stomach tube) at a dose of 0.1 gm. per kilo body weight of albino rats, rabbits and cats. Each experiment consisted of a group of 4 animals whose rectal temperatures were recorded at intervals of $\frac{1}{2}$ hour throughout the day. The first animal was given an intramuscular injection of 1 gm. of peptone per kilo body weight and 2 hours later, when body temperature was rising rapidly to febrile levels, a sulfonamide was given by stomach tube. The second animal was given peptone only. The third animal received no peptone but was given the same sulfonamide and at the same time as animal number one. The fourth animal received neither peptone nor sulfonamides. This experiment was repeated to a total of at least 10 times with each sulfonamide and the mean changes in rectal temperature were then plotted against time.

Results. *Sulfanilamide.* Sulfanilamide had no outstanding effect either upon normal body temperature or upon the febrile temperature of peptone fever in rabbits. A number of normal rabbits showed a slight febrile reaction to sulfanilamide 4 or 5 hours after giving the drug. Sulfanilamide also had no antipyretic action toward peptone fever in albino rats. The rectal temperature of the albino rat was found to decline irregularly during the morning hours and the resulting curves were not as steady as for rabbits. Peptone produced a good artificial fever in cats and sulfanilamide had no antipyretic effect toward this fever. In normal cats, sulfanilamide produced quite a pronounced febrile reaction. These results demonstrate that sulfanilamide in a dose of 0.1 gm. per kilo by mouth, usually the maximal human therapeutic dose, has no antipyretic effect toward peptone fever in albino rats, rabbits and cats but that it may have a febrile effect upon normal body temperature.

Sulfapyridine. The results with sulfapyridine were somewhat variable. In rabbits sulfapyridine sometimes had an antipyretic effect toward peptone fever and at other times no effect. On the average, there was a slight decline in the peptone febrile temperature

after giving this drug. The differences between rabbits may have been due to differences in the rate of gastro-intestinal absorption of the drug since sulfapyridine is well known to be erratically absorbed from the intestinal tract. Sulfapyridine had no effect upon the normal body temperature of rabbits. In the albino rat sulfapyridine had no effect upon normal body temperature nor upon artificial fever induced by peptone. The different responses of rabbits on the one hand and albino rats on the other may be related to the greater susceptibility of rabbits than albino rats to sulfonamides.²

Sulfathiazole. Sulfathiazole in doses of 0.1 gm. per kilo had no effect upon the normal body temperature of rabbits nor upon the febrile temperature of peptone fever. A similar result was obtained in the albino rat.

Sulfadiazine. Sulfadiazine, provided through the courtesy of the American Cyanamid Company, had no antipyretic effect toward peptone fever in rabbits and no effect upon normal rectal temperature in the dose employed.

Sulfaguanidine. Sulfaguanidine was provided through the courtesy of E. R. Squibb and Sons of Canada, Limited, and it was found to have no effect toward peptone fever in rabbits and no effect upon normal body temperature.

Parabenzylsulfanilamide. Parabenzylsulfanilamide was provided by Poulenc Frères of Canada, Limited. It is variously known as Proseptazine, Septazine, M and B 125 and 46 R.P.⁴ In rabbits it had no antipyretic action toward peptone fever and no effect upon normal body temperature.

Parasuccinylsulfanilamide. Parasuccinylsulfanilamide was provided some years ago through the courtesy of Gedeon Richter, Limited, of Budapest, under the name of Ambesid. It had no antipyretic action toward peptone fever in rabbits but produced a definite and marked rise in normal body temperature.

Promin. Promin, the sodium salt of p,p'-diaminodiphenyl-sulfone-N,N'-didextrose sulfonate, was provided through the courtesy of Parke, Davis & Company. It had a slight pyretic effect in normal rabbits but no effect upon peptone febrile temperature.

Sulfacetamide. Sulfacetamide is sulfanilamide with the amide nitrogen acetylated and should not be confused with the acetylated sulfanilamide of blood and urine during sulfanilamide therapy. The latter substance has the acetyl group attached to the para-amino nitrogen. Sulfacetamide was used in Europe in 1938 under the name Albucid and has recently been introduced into Canada under the name Sulamyd; it was provided through the courtesy of Schering (Canada), Limited. It had no antipyretic action toward peptone fever but had a mild febrile effect upon normal rabbits.

Sulfanilyl-dimethylsulfanilamide. Sulfanilyl-dimethylsulfanilamide is one of the disulfanilamides also known as Diseptal C, Disulon and more commonly in Europe as Uleron or Uliron⁴ where it has had extensive trial in the therapy of gonorrhea. It was provided through the courtesy of the Winthrop Chemical Company. It was found to have no effect upon the body temperature of normal rabbits nor upon the febrile temperature of rabbits given peptone.

Azosulfamide. Azosulfamide is the second sulfonamide described by Domagk and is known under various synonyms⁴ such as Pron-tosil Soluble, Neoprontosil and Streptozon-S. It is a red, water-soluble azo compound provided through the courtesy of the Winthrop Chemical Company. It was found to have no effect upon peptone febrile temperature in rabbits but had a pronounced febrile reaction in normal rabbits given by mouth and, as with the other sulfonamides, at a dose of 0.1 gm. per kilo body weight.

Sulfonamide EOS. Sulfonamide EOS is the paramino sodium ethyl sulfonate of sulfanilamide. It is a palatable, water-soluble sulfonamide, especially useful in treating infants. It was provided through the courtesy of Imperial Chemical Industries, Limited, of Manchester, England. This sulfonamide also had no effect upon peptone fever nor upon normal body temperature of rabbits given in doses of 0.1 gm. per kilo by stomach tube.

Summary. Sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfaguanidine, parabenzyisulfanilamide, parasuccinyl-sulfanilamide, promin, sulfacetamide, sulfanilyl-dimethylsulfanilamide, azosulfamide and sulfonamide EOS were given by mouth in doses of 0.1 gm. per kilo body weight to rabbits and, in some instances, albino rats and cats, with an artificial fever induced by the intramuscular injection of peptone and with suitable controls. Body temperature was recorded rectally at intervals of 0.5 hours.

The only sulfonamide which, at this dose, had any antipyretic effect toward peptone fever was sulfapyridine, and it exhibited this effect only upon some rabbits and not at all in albino rats.

Sulfanilamide, parasuccinylsulfanilamide, promin, sulfacetamide and azosulfamide were found to exhibit varying degrees of pyrexia in normal animals.

The authors wish to acknowledge the assistance of Messrs. E. Ewart, Kwong Lee, R. Notman, C. Reich and W. Wigle.

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ALCALIGENES FÆCALIS BACTEREMIA

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THE *Alcaligenes fæcalis* group of organisms is generally classified as being intermediate in their morphologic and cultural characteristics between the colon and the *Brucella* groups. They are generally considered to be saprophytes and non-pathogens.

Petruschky (1896) first isolated the organism from human feces and stale beer. Standard textbooks of bacteriology¹⁸ describe the *Alcaligenes fæcalis* organisms as Gram-negative rods, variable in size and usually larger and thinner than *B. coli* and the ends are less rounded. The organisms are motile and may show peritrichate flagella. Colonies grow well on agar slants and show a raised central portion and a spreading undulate edge. Neither gas nor acid is produced in any of the usual carbohydrate fermentation tests or substrates. Litmus milk is rendered alkaline and a brown pigment is produced on potato media which is characteristic. However, it is generally conceded that these organisms are not a sharply defined group.¹²

Pathogenicity. It seems to be well established that *Alcaligenes fæcalis* on occasion can be definitely pathogenetic. It may give rise to a variety of disease conditions. For example, meningitis has been reported by Spray and Hawk,¹⁶ also by Gatewood,³ and Mason.⁹ Anderson¹ cultured the organism from the blood of 2 patients who exhibited a syndrome simulating rheumatic polyarthrititis. The organism was found in the blood of a patient with acute hepatitis and jaundice by McIntyre.¹⁰ An *Alcaligenes* type bacillus was cultured from the blood of a patient with a typhoid-like state by Hazen and Mortillaro,⁵ and others,¹⁴ and also from cases of acute gangrenous appendicitis by Emil Weiss.²⁰ It was considered the cause of death in a case of protracted sepsis reported by Goldberg.⁴ Gall stones² and a renal calculus¹⁷ were found to harbor the organism. The bacillus has been considered the pathogenic agent in certain types of infant summer diarrheas¹⁹ as well as the cause of a few cases of adult enterocolitis.¹⁵ Positive stool cultures have been reported in a few cases of convalescing typhoid fever and bacillary dysentery.⁶ The close morphologic and cultural relationship between certain strains of the *Bacillus alcaligenes* group and the bacillary organisms associated with dog distemper has been pointed out.¹³

Case Report. The patient, a white male, aged 36, was admitted to the hospital on June 15, 1941, complaining of diffuse epigastric pain and fever

of 3 days' duration. His wife and 5 children were in good health. He had worked as a baker during his entire adult life in a small town north of New Orleans.

On physical examination his temperature was 101.6°, pulse 110, B.P. 125/80, and respiration 20. He was well developed and well nourished. There was no lymphadenopathy. The heart and lungs were negative. No abdominal tenderness could be elicited and the spleen could not be palpated. The genitalia and the extremities were likewise negative.

During his first hospital stay which lasted about 8 weeks the patient had a remitting type of fever which ranged from 99° in the morning to 101° to 103° in the evening. Several times a week the patient experienced shaking chills. The epigastric pain lasted 3 days and was followed by a dragging sensation in the left hypochondrium which persisted in a varying degree for 18 days. The spleen was palpable for a short time during this period.

Agglutinations for typhoid, paratyphoid, undulant fever, tularemia and bacillary dysentery were negative. The skin test for undulant fever was negative; the urine and stool were negative, on culture as well as microscopic examination.

The red blood cell count was 3,660,000 and the hemoglobin 12 gm. The white blood cells numbered 5400 (60% neutrophils with a moderate shift to the left). Multiple smears of the blood were negative for malaria. The chest Roentgen ray film was negative. Of 6 blood cultures, 4 yielded no growth, but 2, collected on July 16 and 17, were positive for an organism which grew well on brain broth, 5% dextrose agar, lactose agar, and beef infusion agar. The organisms were slightly motile Gram-negative rods which showed moderate variation in size. No fermentation occurred in dextrose, lactose, sucrose, maltose, mannite, rhamnose, xylose or dulcital. Litmus milk was alkalized in 4 days, and gelatin was slightly liquefied in 24 hours. The colonies on agar were discrete and grayish and 1 to 2 mm. in diameter in 24 hours. On the basis of these findings the organisms were tentatively classified as belonging to the *Alcaligenes fæcalis* group. An agglutination test using the patient's serum and the culture organisms was found to be negative. As the attending staff felt that these organisms were probably contaminants, and the clinical picture closely resembled malaria, it was decided to try a course of quinine. Quinine sulphate was given in therapeutic doses. There was a sudden drop in the patient's temperature to normal which lasted until the time of discharge on August 15. He was instructed to continue quinine medication at home.

The patient was readmitted to the hospital on August 21, 1941. He stated that while at home he was without fever for 2 days, then the fever (102°) returned each afternoon, preceded by a chill. After 3 days of chills and fever, he decided to return to the hospital. During this second admission which lasted 39 days, the patient's condition grew progressively worse. Anemia, toxemia and anorexia were now present and there occurred a 30 pound loss in weight.

The red blood cell count was 3,300,000; hemoglobin 9 gm. The white blood cell count was 8000 (82% neutrophils). The urine showed occasional granular casts and a few white blood cells and red blood cells. Cystoscopy was performed on September 4, because the patient had complained of tenderness in his right flank. Urine cultures from each kidney and retrograde pyelograms proved negative. Proctoscopy revealed a normal bowel. The tuberculin test 1 to 1000 O.T. was also negative. The agglutinations were repeated and again found negative. The skin test and the opsonocytophagic index for undulant fever were again reported negative. Six blood cultures failed to show a growth but 2 were positive for an organism having the characteristics of *Bacillus alcaligenes fæcalis*.

The patient was given sulfanilamide 60 gr. for 3 days then 30 gr. daily thereafter. There was a drop in temperature to normal for 3 days with a subsequent evening elevation of about 100°. The patient was discharged on September 29 with a low-grade fever. Sulfanilamide was discontinued on the day of discharge.

The patient remained at home for 20 days and the fever continued with a small afternoon rise to 100°. Eight days before the third admission the fever reached 105° and was associated with chills and sweats. On October 20 he again sought admission. At varying times while at home he experienced severe aching pain of the left chest with the ascent of fever. Later there was aching of the left fourth toe and small toe but no swelling of the joints. The ball of the left foot was swollen and tender for 2 days.

On admission the spleen could be palpated and a soft systolic murmur could be heard at the apex. Sulfanilamide was started the day after admission but was discontinued 13 days later as it seemed ineffective. For 10 days he received no medication and then sulfadiazine 15 gr. q.i.d. was begun and continued until time of discharge on December 19. There was a drop in the temperature to normal 8 hours after the initial dose, and except for slight elevations to 100° on 3 occasions, it remained normal. During the time that the patient was receiving sulfanilamide medication he had pain and swelling of the right ankle joint which lasted 2 days. Five days later there was tenderness and pain of the left knee and hip joint but no swelling. This subsided in 3 days. Swelling and pain of the first and second right metacarpophalangeal joints were present on November 15 and 16, during sulfadiazine therapy.

On November 29 the patient complained of headache and on the following day the headache was more severe with definite stiffness of the neck and suggestive Kernig's and Brudzinski's signs were present. Spinal puncture revealed a pressure of 250 mm. of water with normal mechanics. The fluid was hazy and contained 1000 cells per c.mm. with 65% polymorphonuclears and 25% lymphocytes and 10% unidentified cells. No organisms were present on smear or culture. Fever of 100° to 101° was present, but 2 days later the temperature was normal, and 4 days later all suggestive meningitic symptoms had disappeared.

During the third and last admission all of the usual laboratory procedures were repeated. This included agglutinations, urine and blood counts. All were reported normal. Six blood cultures were done and all were negative except one obtained on October 20. This culture was positive for *B. alcaligenes fæcalis* which made a total of 5 positive blood cultures for this organism. Gastro-intestinal Roentgen rays were normal and roentgenograms of the joints and large bones were negative.

The patient was discharged on December 19 as afebrile and with no complaints. During the 2 weeks prior to discharge he had gained 15 pounds in weight. He was readmitted on January 31, 1942, for a checkup. The patient was afebrile. The blood counts were normal. There had been a progressive gain in weight and the patient felt well.

Comment. This case is of interest because of the long duration (4 months) of the febrile course and the multiplicity of the symptoms. In the majority of the other cases reported in the literature which we were able to study, the duration of the septicemia ranged from 2 weeks to 2 months. The striking symptoms in our case were the shifting polyarthritides which developed during October and involved successively the toes of the left foot, right ankle joint, left knee and hip joints and the right metacarpophalangeal joints. These symptoms closely resembled those reported as occurring in

Anderson's cases.¹ The joints showed local redness, heat, pain, and slight swelling but there was no evidence of joint damage. Of interest also were the development of signs and symptoms as well as laboratory evidence of meningitis which occurred during the second week of sulfadiazine therapy. In the 3 reported cases of *Alcaligenes fæcalis* meningitis, 1 occurred following an otitis media,¹⁶ another complicated a meningocele,⁹ and the third followed a craniotomy.³ These cases suggest the possibility that trauma to the central nervous system paved the way for invasion by the mildly pathogenic *Alcaligenes fæcalis* although this was not true in our case.

Many reports have pointed out the similarity between *B. alcaligenes fæcalis* septicemia and mild typhoid and paratyphoid fever. In our case, the persistent fever, slowly progressive toxemia, low white count, mild anemia, splenomegaly, and increased erythrocyte sedimentation rate were all suggestive. Marshall⁸ has stated that many cases of clinically mild typhoid or paratyphoid fever which the laboratory fails to confirm, if studied carefully, will prove to be *Alcaligenes fæcalis* infections. We are inclined to agree with this statement. It is of interest to note that Ravenel¹⁴ reported finding lesions typical of early typhoid fever in an autopsy of a patient dying of *Alcaligenes fæcalis* bacteremia.

At various times during his illness the patient had pain in the right flank, and on November 13 the urine was reported positive for white and red blood cells. The same findings were noted on several subsequent examinations and although repeated urine cultures were negative, we felt we were justified in assuming that a low-grade urinary infection was present, which was probably due to the same organism isolated from the blood stream. Stuart, Thompson and Krikorian¹⁷ reported a case of urinary tract infection in which the organism was cultured from the urine; they were also successful in isolating the *B. alcaligenes fæcalis* from a stone removed at operation from the left kidney.

Many bacteriologic texts express doubts that specific agglutinins develop in patients with *B. alcaligenes fæcalis* infections; however, Wyatt and Stuart,²¹ also Thompson and Krikorian¹⁷ and others have found agglutinins present in low titer. Our case did not show agglutinins.

We are at a loss to explain the varied responses to the therapeutic agents used. Quinine was used empirically with what was thought at first to be a good result; however, the subsequent course of the illness proved rather definitely that this drug was of no value, and that the drop in temperature was not due to the specific effect of the quinine. Sulfanilamide was without any prolonged effect since fever as well as other symptoms of the illness persisted in spite of the presumably adequate dosage.

All symptoms of the illness promptly disappeared after the administration of sulfadiazine. This of course excepts the episode

of meningitis which occurred after 18 days of sulfadiazine therapy. Five blood cultures have been reported negative since the use of the drug, and on follow-up examinations during a 3-month period, the patient has been found to be asymptomatic. However, it is a question in our minds whether sulfadiazine had anything specific to do with the ultimate recovery of the patient.

Summary and Conclusions. A case of bacteremia due to a *Bacillus alcaligenes faecalis* type organism has been presented. The bacteremia and fever lasted for 4 months; the interesting manifestations were a polyarthritis and meningitis. Following the use of sulfadiazine the symptoms disappeared and the blood cultures became sterile.

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THE EFFECT OF THE HYDROGEN-ION AND STARCH CONCENTRATION OF THE SUBSTRATE ON SERUM AMYLASE AND AMYLASE-ACCELERATOR OF SERUM

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A STARCH-SPLITTING ferment, diastase, or more accurately, amylase, was first found in the blood by Magendie in 1846.⁷ It apparently is partly or wholly of pancreatic origin, and its amount is increased by ligation of the pancreatic ducts,⁶ and is increased or decreased by pancreatic disease, cysts and tumors.^{3,4,5,13,14}

The great variability in the observations on the amylase content of the blood serum may be ascribed, in part at least, to the various methods used,⁴ and especially by the reaction and the concentration of the substrate. As may be seen in Table 1, in which are

TABLE 1.—EFFECT OF THE HYDROGEN-ION CONCENTRATION ON THE STARCH-LIQUEFYING AND AMYLASE-ACCELERATING ACTIVITY OF NORMAL HUMAN SERUM.

pH of starch substrate	Percentage concentration of starch substrate (and date of titration)	Amylase units ^a in normal human serum (per cc.)	Amylase units per cc. of duodenal contents ^b	Amylase units in same duodenal contents + 0.3 cc. normal human serum ^c	Amylase-accelerating units per cc. of normal human serum	Percentage increase in amylase units produced by 0.3 cc. normal human serum
3.0	6 (1/9)	+h	+h			
4.0	6 (1/9)	+				
4.8	6 (2/13)	0	30.8	204.0f	571.6	562
5.0	6 (1/16)	0	27.0	102.4g	248.8	280
5.6	2 (12/1)	11.3				
5.7	4 (2/4)	+	141.2	296.4	512.2	110
5.7	6 (1/7)	+	75.0c	80.0c	16.5	7
6.0	6 (1/9)	1.5				
6.2	6 (1/13)	+	141.2	200.0f	194.0	41
6.2	6 (1/16)	..	160.0	184.4g	80.5	15
6.3	4 (2/4)	..	204.2	235.2	102.3	15
6.4	6 (1/9)	0				
6.8	4 (2/4)	..	214.4	300.0	282.5	40
7.0	6 (1/9)	+				
7.0	4 (2/9)	+	220.8	371.2	496.3	68
7.0	4 (2/16)	+	31.1d	79.4	159.4	155
7.2	6 (1/13)	+	220.0	120.0f	-330.0	-45
7.2	6 (1/16)	+	150.0	252.8g	339.2	69
7.3	4 (2/4)	..	207.2	287.2	266.6	39
7.8	6 (1/13)	..	120.0	80.0f	-132.0	-33
7.9	6 (1/16)	+	75.0	141.2g	218.5	88
8.0	6 (1/9)	14.2				
8.0	4 (2/4)	..	77.6	196.8	393.4	154
8.6	6 (1/13)	+	47.2	80.0f	108.2	69
8.6	6 (1/16)	..	45.0	84.0g	128.7	87

a A unit of amylase is the amount which requires 60 minutes to produce a 20% reduction in the viscosity of a starch substrate.^{5,8,12}

b 0.1 cc. of duodenal contents (except 2 titrations *c, d*) and 0.3 cc. water were added to 10 cc. of 2% to 6% starch suspensions and the amylase activity determined viscometrically at 34° C.^{5,8,12} The duodenal contents were collected 12/3 from an infant, kept in a refrigerator, and diluted 1 to 4 with saline before being titrated (H. L. H. No. 40773, 18 months of age, normal digestion, diarrhea during the previous summer).

c Amylase units per cc. of 1% taka-diastase (diluted with saline). In the serum amylase-accelerating titration, the enzyme and serum were mixed 15 minutes before being added to the starch suspension.

d Amylase units per cc. of 0.2% holadin (diluted with saline).

e 0.1 cc. of the same duodenal contents *b* and 0.3 cc. pooled normal human serum were mixed and (except in 11 titrations *c, f, g*) immediately added to 10 cc. of 2% to 6% starch suspensions, and the amylase-accelerating activity determined viscometrically at 34° C.⁹

f The amylase activity of 0.3 cc. serum was titrated for 90 to 120 minutes at 34° C., and then 0.1 cc. duodenal contents was added to the mixture, and its amylase activity retitrated at 34° C. The final reaction of the pH 4.8 mixture was pH 5.6, and that of the pH 8.6 mixture was pH 8.2.

g 0.1 cc. of the duodenal contents was mixed with 0.3 cc. pooled normal human serum 30 minutes before being added to the starch suspensions.

h + indicates that amylase was present, but that it was less than 1 unit per cc.

tabulated the results of 25 viscometric titrations^{2,8,12} of the amylase in pooled normal human serum at hydrogen-ion concentrations from 3.0 to 8.6, the amount of serum amylase is irregularly affected by the reaction of the substrate. At pH 4.8, 5.0, and at 6.4, no serum amylase could be demonstrated, and only at pH 5.6, 6.0 and 8.0 were the amounts sufficient to record in units.^{2,8,12} The variation in these results also was increased by differences in the concentration of the substrate (2% to 6% starch).

In addition to amylase, human serum contains an amylase-accelerator,^{1,9,10,15} *i. e.*, the addition of serum to duodenal contents increases their starch-liquefying activity to a greater degree than can be explained by the amylase content of the added serum (Table 1). This amylase-accelerating strength of normal human serum is greatest at pH 4.8. Large amounts also are present at pH 5.0, 5.7, 7.0 and 8.0; it is apparently absent at pH 7.2 and 7.8. The optimal reaction of human duodenal contents is pH 7.0.¹¹

Conclusion. Serum amylase and amylase-accelerator results in order to be comparable should be obtained by titrations made at the same reaction, and with the same preparation and concentration of starch.

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THE SIGNIFICANCE OF THE SO-CALLED P-PULMONALE PATTERN IN THE ELECTROCARDIOGRAM*

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THE clinical recognition of cardiac involvement due to chronic lung disease has recently been aided by radiologic studies,²⁷ includ-

* Aided by the A. D. Nast and Emil and Fanny Wedeles Funds for Cardiovascular Research.

ing direct visualization^{28,36} of the chambers of the heart, and by the use of ether for determination of the pulmonary circulation time.²⁵ However, little attention has been paid to the electrocardiogram in this condition. The majority of authors^{2,4-9,11,21,30,35,37,39} reporting on the electrocardiogram have discussed the presence or absence of changes in the ventricular complex indicative of strain on the right ventricle. The first to draw attention to the occurrence of typical changes in the P waves in bronchial asthma was Kahn.¹⁶ M. Winternitz¹⁰ described a characteristic pattern of the P wave in the limb leads, consisting of a small upright P in Lead I and tall upright peaked P waves in Leads II and III, all of normal duration; this combination was designated as P-pulmonale and the changes were attributed to strain on the right auricle. This contour contrasts with the broad notched upright P₁ and P₂ characteristic of left auricular strain seen particularly in cases of rheumatic mitral stenosis.

This P-pulmonale pattern has in recent years been noted by various authors,^{10,12-14,17,18,20,23,24,26,27,29,31,33} but there has been no unanimity as to its frequency or diagnostic significance. Parkinson and Hoyle²⁷ found this pattern in only 4 of the 60 cases of emphysema. Harkavy and Romanoff¹⁴ described 15 such cases in their series of 50 patients with bronchial asthma and drew attention to the transitory nature of this contour which occurred only during the asthmatic attack in the majority of cases. Nordenfelt^{23,24} denied the specific significance of this P pattern and claimed that such P waves occurred frequently in the absence of pulmonary disease in individuals having a labile sympathetic nervous tone.

This discrepancy in the literature suggested the present study in which the incidence, constancy and diagnostic value of this P-wave pattern was analyzed by selecting 50 consecutive cases with this contour and determining the clinical and, where available, the autopsy findings.

Criteria Employed. The 50 consecutive records were obtained from the routine tracings taken in the Heart Station during the past 2 years which fulfilled the following criteria:

1. P waves of normal duration (less than 0.12 second) and without notching.
2. P₂ taller than P₁.
3. P₁ small and upright (less than 1.5 mm.).
4. P₂ and P₃ tall and peaked (greater than 2 mm.).
5. P in CF₂ inverted and greater than 1.5 mm.
6. P in CF₄ inverted.

TABLE 1.—CLINICAL AND ROENTGEN RAY CORRELATION IN 50 CASES SHOWING THE P-PULMONALE PATTERN

Clinical evidence of pulmonary disease		Roentgen ray evidence of pulmonary disease			Clinical and/or Roentgen ray evidence of pulmonary disease	
Yes	No	Yes	No	No films taken	Yes	No
35	15	32	10	8	40	10*

* No films taken in 3 cases.

TABLE 2.—POSTMORTEM CORRELATION OF CHRONIC PULMONARY DISEASE IN 8 AUTOPSIED CASES OF P-PULMONALE

Case	QRS in limb leads	Deviations of S-T segment	Pathologic findings in heart			Other findings	Pulmonary pathologic findings
			Wall, left vent., cm.	Wall, right vent., cm.	Wt., heart, gm.		
1	Left ventricular preponderance	...	1.0	0.1	340	Moderate coronary sclerosis. Fatty infiltration of myocardium of right ventricle	Pulmonary emphysema. Healed apical tuberculosi.
2	Small QRS ₁ ; diphasic QRS ₂ and QRS ₃ and deep S ₂ and S ₃	...	1.0	0 2-0 3	400	Hypertrophy and dilatation of right auricle and ventricle	Pulmonary emphysema. Moderate pulmonary arteriosclerosis.
3	No axis deviation	S-T ₂ and S-T ₃ depressed	1 2	0 1	175	Brown atrophy	Pulmonary emphysema.
4	Right axis deviation	S-T ₂ and S-T ₃ depressed	1 2	...	200	Hypertrophy of right ventricle. Brown atrophy of left ventricle	Bronchiectasis. Pulmonary emphysema.
5	Small QRS ₁ ; diphasic QRS ₂ and QRS ₃ and deep S ₂ and S ₃	...	1 0	0 3-0.8	300	Marked hypertrophy and dilatation of right ventricle. Dilated left auricle. Enlarged pulmonary conus	Pulmonary emphysema.
6	Small QRS ₁ ; diphasic QRS ₂ and QRS ₃ and deep S ₂ and S ₃	500	Hypertrophy and dilatation of right ventricle. Obliteration of pericardial sac. Myocardial fibrosis	Pulmonary emphysema. Pulmonary arteriosclerosis.
7	Small QRS ₁ ; diphasic QRS ₂ and QRS ₃ and deep S ₂ and S ₃	...	1 4	0 2-0 4	360	Moderate hypertrophy of right and left ventricle. Fatty infiltration of right ventricle	Pulmonary emphysema.
8	No axis deviation	S-T ₂ and S-T ₃ depressed	1 4	0 2	350	Moderate coronary sclerosis. Myocardial fibrosis	Pulmonary emphysema.

Results. The results are summarized in Tables 1, 2 and 3. In Table 1 is shown the frequency of clinical and Roentgen ray evidence of pulmonary disease. In Table 2, the necropsy findings in 8 cases are presented.

TABLE 3.—ANALYSIS OF THE VENTRICULAR COMPLEX IN 50 TRACINGS SHOWING P-PULMONALE PATTERN*

Right ventricular preponderance	11
Right axis shift	13
With depressed S-T in Leads II and III	7
Without depressed S-T in Leads II and III	6
Left axis shift	3
Left ventricular preponderance	5
No axis shift	10
With depressed S-T in Leads II and III	7
Without depressed S-T in Leads II and III	3
Small QRS ₁ with diphasic QRS ₂ and QRS ₃ and deep S ₂ and S ₃	5
Intraventricular block	3
S type	2
Common type	1
Total	50

* Patterns are described in Katz.¹⁷

The pattern of the ventricular complexes in the 50 cases of P-pulmonale are listed in Table 3. Right ventricular preponderance, characterized by a mainly inverted QRS in Lead I with a prominent S wave, was present in only 11 cases (Fig. 1 *A* and *B*, Fig. 3 *A*). However, depression of the S-T segment in Leads II and III, which may be an indication of right ventricular strain, occurred in 7 of 13 cases of right axis shift (Fig. 1 *C*) and in 6 of the 10 cases without axis deviation (Fig. 3 *B*). The evaluation of such S-T depressions is, however, difficult since the tall P_2 and P_3 tends to be followed by a prominent auricular T wave causing a depression of the P-Q segment which extends into and depresses the S-T segment. Furthermore, in some cases, digitalis and/or coronary insufficiency had to be considered as a possible cause of the S-T depressions. Low "voltage" in the limb leads was present in 1 case, and a tendency to low "voltage" in 5 additional cases (Fig. 1 *C*).

Leads CF_2 and CF_4 were available in all cases. P was inverted in both leads, more deeply in position C_2 than in C_4 (Fig. 1 *A*, *C*, *D* and *E*, Fig. 2 *A* and *B*, Fig. 3 *A* and *B*). In contradistinction to the prolonged diphasic, and unusually large P in mitral stenosis, in P-pulmonale the auricular wave in CF_2 consists of a single inverted phase of normal duration.

Analysis of the 50 cases showing the P-pulmonale pattern in the electrocardiogram revealed evidence of chronic pulmonary disease on clinical and/or roentgenologic examination in 40 instances (Table 1). Right ventricular preponderance was present in only 9 instances. Chronic cor pulmonale is often associated with hypertension or coronary disease which in itself leads to left ventricular hypertrophy, and in such cases there is a combination of right and

left ventricular strain. Furthermore, Scott and Garvin³⁴ have shown in a series of 50 autopsied cases of cor pulmonale that even in the absence of an associated hypertension, coronary sclerosis, or valvular lesion, hypertrophy of the muscle was not limited to the right ventricle alone, but occurred simultaneously in both. This may explain the low percentage of right ventricular preponderance found

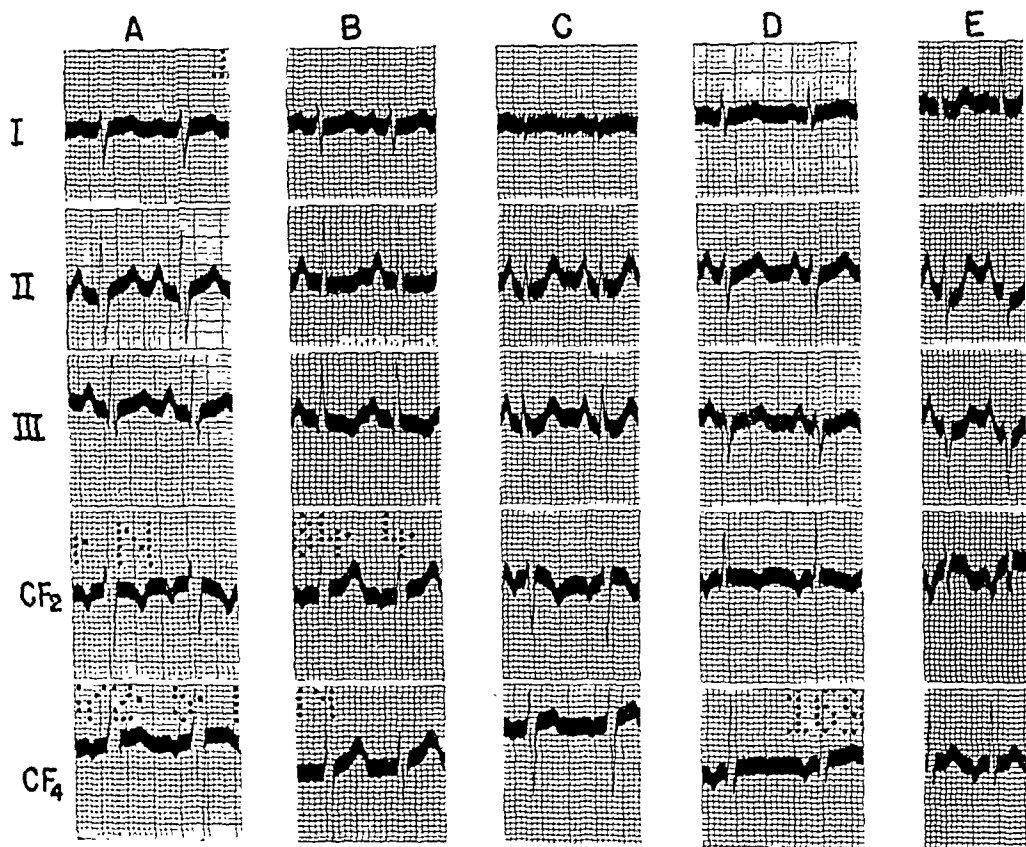


FIG. 1.—Five examples of P-pulmonale and the chest lead equivalent associated with P-pulmonale. Discussed in text. *A*, A case of pulmonary emphysema shows right ventricular preponderance and T inversion in CF_2 . *B*, A case of bronchial asthma also shows right ventricular preponderance. *C*, A case of pulmonary emphysema shows right axis shift with marked S-T depression in leads II and III as well as T inversion in CF_2 . *D*, A case of bronchiectasis and arteriosclerotic heart disease shows small QRS_1 and diphasic QRS_2 and QRS_3 with deep S_2 and S_3 as well as QRS upright and T inverted in CF_2 . *E*, A case of pulmonary emphysema shows left ventricular preponderance of the mixed type with marked S-T depression in Leads II and III as well as small QRS and inverted T in CF_2 .

in our series. The combination of right and left heart strain may give rise to the peculiar pattern observed in 5 cases, characterized by a small diphasic QRS in Lead I, and a mainly inverted diphasic QRS in Leads II and III with deep S_2 and S_3 (Fig. 1 *D*). This configuration resembles the QRS limb lead pattern produced by anterior wall infarction but can be differentiated from it.¹⁵:-

In the 10 cases of P-pulmonale without clinical or Roentgen ray

evidence of pulmonary disease the QRS duration and "voltage" were normal. The ventricular complex was normal in 5 cases. One case showed the pattern of anterior wall infarction, 1 showed changes suggestive of acute cor pulmonale (middle tracing of Fig. 2 *B*), 1 had S-T depressions in Leads II and III (Fig. 3 *B*) and 2 showed right ventricular preponderance.

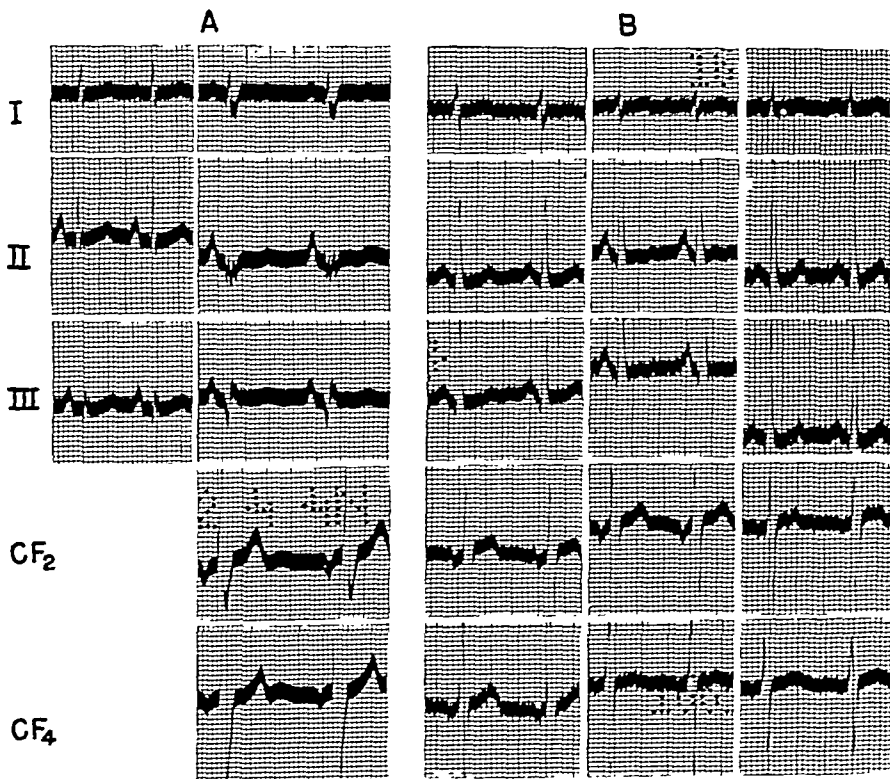


FIG. 2.—*A*, The 2 records of P-pulmonale were taken in a case of bronchial asthma and pulmonary emphysema, 9 years apart. The first record shows P-pulmonale with left axis shift. The second record shows the persistence of the P-pulmonale with its chest lead equivalent and the development of intraventricular block of the S-type. Discussed in text. *B*, The 3 records are from a case of postoperative pulmonary embolism. In the first record, taken within a few hours of the clinical episode there is a right axis deviation. This persists in the second record taken 6 days later, and is associated with T-wave changes and the development of P-pulmonale and its equivalent in CF₂. Practically all these deviations have disappeared in the third record taken 2 weeks after the second, confirming the view that all the changes including those of the P wave were due to an acute cor pulmonale. Discussed in text.

The 10 cases with P-pulmonale but without evidence of chronic pulmonary disease included a case of congenital heart disease with pulmonic stenosis (Fig. 3 *A*), 1 of carcinoma of the rectum with a clinical episode diagnosed as pulmonary embolism (Fig. 2 *B*), 1 of recent myocardial infarction of the anterior wall pattern, 1 of hyper-

thyroidism, and 6 cases diagnosed as psychoneurosis or psychosis (Fig. 3 *B*). In the first 3 of the 10 cases, it is possible to explain P-pulmonale on the basis of permanent pulmonary hypertension (pulmonic stenosis) or transient pulmonary hypertension (acute cor pulmonale, recent myocardial infarction) leading to right auricular strain.* In the remaining 7 cases, however, the change in the

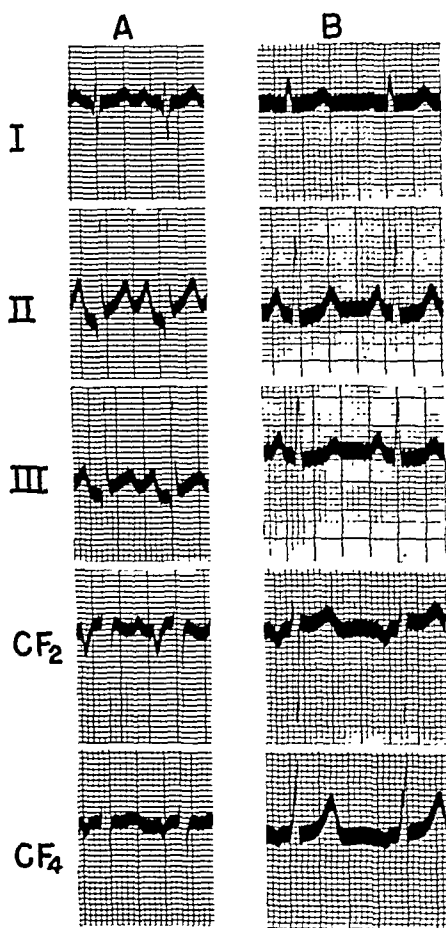


FIG. 3.—*A*, A case of congenital heart disease with right ventricular preponderance and P-pulmonale and its equivalent in CF_2 . In this 19 year old male there was no evidence of pulmonary disease or abnormality. Discussed in text. *B*, A case of psychoneurosis without evidence of cardiac or pulmonary disease showing, besides S-T depression in Leads II and III and QRS almost entirely inverted in CF_2 , the P-pulmonale pattern and its chest lead equivalents. Discussed in text.

auricular electrocardiogram must be attributed to some other factor. Perhaps Nordenfelt²³ is correct in his view that this P pattern occurs for some reason in individuals having a labile autonomic nervous system such as might occur in our group of mentally dis-

* The Editor is of the opinion that in addition to changes in position, cor pulmonale may be caused by any condition that raises right intra-auricular pressure sufficiently, whether primarily in the pulmonary artery, the lungs, the left auricle or even further "downstream." In experiments performed over 25 years ago²² partial clamping of the pulmonary artery brought out this point.—EDITOR.

turbed patients. However, another factor, altered position of the heart, should also be considered. A study of routine tracings taken in the Heart Station on psychotic patients prior to shock therapy revealed that P-pulmonale is more common in patients with an asthenic habitus than in those of a sthenic build. This would seem to indicate that the asthenic habitus with the low diaphragm and centrally located heart is the important factor in imitating P-pulmonale, rather than any supposed abnormality of the autonomic nervous system.

The question follows as to what rôle an altered position of the auricles might play in the production of P-pulmonale in cases of chronic pulmonary disease. It may be seen in previously published articles^{1,24,32,38} that changes in position from the recumbent to the sitting, particularly in young asthenic individuals with centrally placed hearts will produce alterations in the auricular complex similar to the P-pulmonale. These changes may be accompanied by a prominent S in Lead I, depressed S-T segment in Leads II and III, and an inverted T_2 and T_3 , thus imitating in its entirety the pattern of chronic cor pulmonale.

The asthenic individual and the typical case of cor pulmonale, on fluoroscopic examination, both show a low diaphragm with an abnormal position of the auricles. Hence it is quite possible to attribute the P-pulmonale pattern to such an altered auricular position without necessarily assuming involvement of the auricular muscle. In chronic cor pulmonale, fluoroscopy often fails to reveal the right auricular enlargement which is expected with right auricular involvement.^{5,27} This lends further support to the belief that this P pattern is due mainly to the abnormal position of the auricles associated with chronic pulmonary emphysema, pulmonary fibrosis, bronchiectasis, and other chronic lung affections.

The available postmortem studies regarding auricular involvement in chronic cor pulmonale^{3,19,40} are equivocal, and further anatomic examinations from this point of view are necessary to estimate the rôle of position of the auricle in the P-pulmonale pattern. While these observations on auricular position as a cause of these P-wave changes show that this pattern may be found in cases without pulmonary disease, nevertheless, analyses reveal that the P-pulmonale is suggestive of chronic lung involvement if the asthenic build can be ruled out. The P-pulmonale pattern together with a right ventricular preponderance and/or "low voltage," represents the characteristic electrocardiogram of chronic cor pulmonale, although as evidenced by our series not all these characteristics are seen in every case.

Summary. 1. Fifty consecutive cases of P-pulmonale were studied in order to determine the significance of this P-wave pattern.

2. In 40 cases there was clinical and/or Roentgen ray evidence of chronic pulmonary disease as suggested by the auricular electro-

cardiogram. The 10 exceptions were 1 each of congenital heart disease, acute cor pulmonale, recent myocardial infarction, hyperthyroidism, and 6 cases with the diagnosis of psychosis, or psychoneurosis without cardiac or pulmonary involvement.

3. Eight cases of P-pulmonale with autopsy control were all found to have anatomic evidence of chronic pulmonary disease.

4. The P-pulmonale pattern occurs in individuals of asthenic habitus without evidence of cardiac or pulmonary involvement.

5. The characteristic P-pulmonale in the chest Leads CF_2 and CF_4 is an inverted P-wave of normal duration in cases showing P-pulmonale in the limb leads.

Conclusions. 1. The P-pulmonale pattern is not pathognomonic of chronic pulmonary disease, since it occurs in its absence, as it appears in a variety of other conditions.

2. P-pulmonale in association with low "voltage" in the limb leads or with right ventricular preponderance represents the characteristic electrocardiogram of chronic cor pulmonale.

3. It is of diagnostic importance to distinguish the P-pulmonale pattern from that seen in rheumatic mitral stenosis. The P-wave pattern can be used as a diagnostic hint in determining the cause of right ventricular preponderance if both are found in the same record.

4. Further anatomic and Roentgen ray correlation studies are necessary to establish definitely whether P-pulmonale is due to altered position, increased strain on, or hypertrophy of the right auricle.

We are indebted to the several physicians of the hospital staff for permission to report their cases, to Dr. O. Saphir of the Department of Pathology, for his necropsy report on the cases used in this study, and to Dr. L. N. Katz for his advice and suggestions in the preparation of this paper.

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"ESSENTIAL" HYPERTENSION. A CONCEPT OF ITS MECHANISM*

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RECENT studies have suggested that a substance can be obtained from renal tissue which is effective in lowering elevated blood pressure.^{14,27} Because this material seems of therapeutic value there is need to reëxamine the problem of arterial hypertension, to define its nature and to appraise the various factors which contribute to its development.

Arterial hypertension is probably not the result of a single factor.³⁷ Although the blood pressure may become chronically elevated through mechanisms which are in most instances similar, the various influences which initiate these mechanisms are in all likelihood different. It is the purpose of this report to identify these influences so that they may be studied separately. It is also desirable that those which have been investigated experimentally be related to their clinical counterparts.

The experimental evidence points to the kidneys as having a

* Read before the New Haven County Medical Society, March 5, 1941.

causal relation to the condition. While there are occasional cases in man resembling the non-renal hypertension of animals, in most instances the kidneys likewise seem to be involved in some manner, directly or indirectly. This discussion will deal, therefore, with concepts based on this hypothesis and will assume that *renal ischemia*¹⁰ constitutes the occasion for the existence of hypertension and initiates its development in most circumstances.

It is necessary that the phrase "renal ischemia" be defined. As used in this discussion it has the meaning given to it by Goldblatt,¹⁰ implying less arterial blood in the kidneys due to an increase in resistance to the flow of blood through the kidneys. When a renal artery is partially constricted, or the lumina of the afferent arterioles narrowed, blood flow depends upon: 1, the degree of constriction; and, 2, the systemic blood pressure, as long as other factors (viscosity of blood, cardiac output, blood volume) remain constant. If No. 1 causes an increase in No. 2, and No. 2 becomes elevated enough to overcome the increased resistance caused by No. 1, the kidney will no longer be ischemic. If then the factors giving rise to the constriction remain unchanged, the kidney retains the capacity for becoming ischemic should the blood pressure fall. If the constriction is great enough to overcome increased blood flow caused by a rise in blood pressure, the kidney will remain ischemic, although less than if blood pressure were unchanged. Renal ischemia, by actual measurement therefore, may or may not be present when the blood pressure is elevated, even though the conditions giving rise to it continue to act. Narrowing of the efferent arterioles, which causes ischemia of the tubular vessels, may also result in diminution of total blood flow.

The influences which are at work in arterial hypertension include: A, a *Constitutional Factor*, an unknown defect suggested by the frequent presence of similar cases in the family histories of patients; B, the *Causes of Renal Ischemia*, such as are known in man and in animals; C, the *Mechanism of Hypertension*, as suggested by the available evidence; and, D, the *Effect of Elevated Blood Pressure*, as seen by clinical and pathologic examination. To simplify discussion, these elements have been arranged in Figure 1.

A. The Constitutional Component of Arterial Hypertension. Certain findings suggest that individual susceptibility is an important factor in causation. First, the condition appears to be hereditary in a large percentage of cases,¹⁵ since arterial hypertension is present in the families of most patients exhibiting it. The children of hypertensive parents often react in an exaggerated fashion to tests of vascular irritability, even when their blood pressures are normal.¹⁶ Those who do are, in fact, more liable to develop hypertension later in life than are others who react normally.¹⁷

Second, individuals exhibiting "early" or "mild" arterial hypertension are for the most part of the "nervous type."³² They are

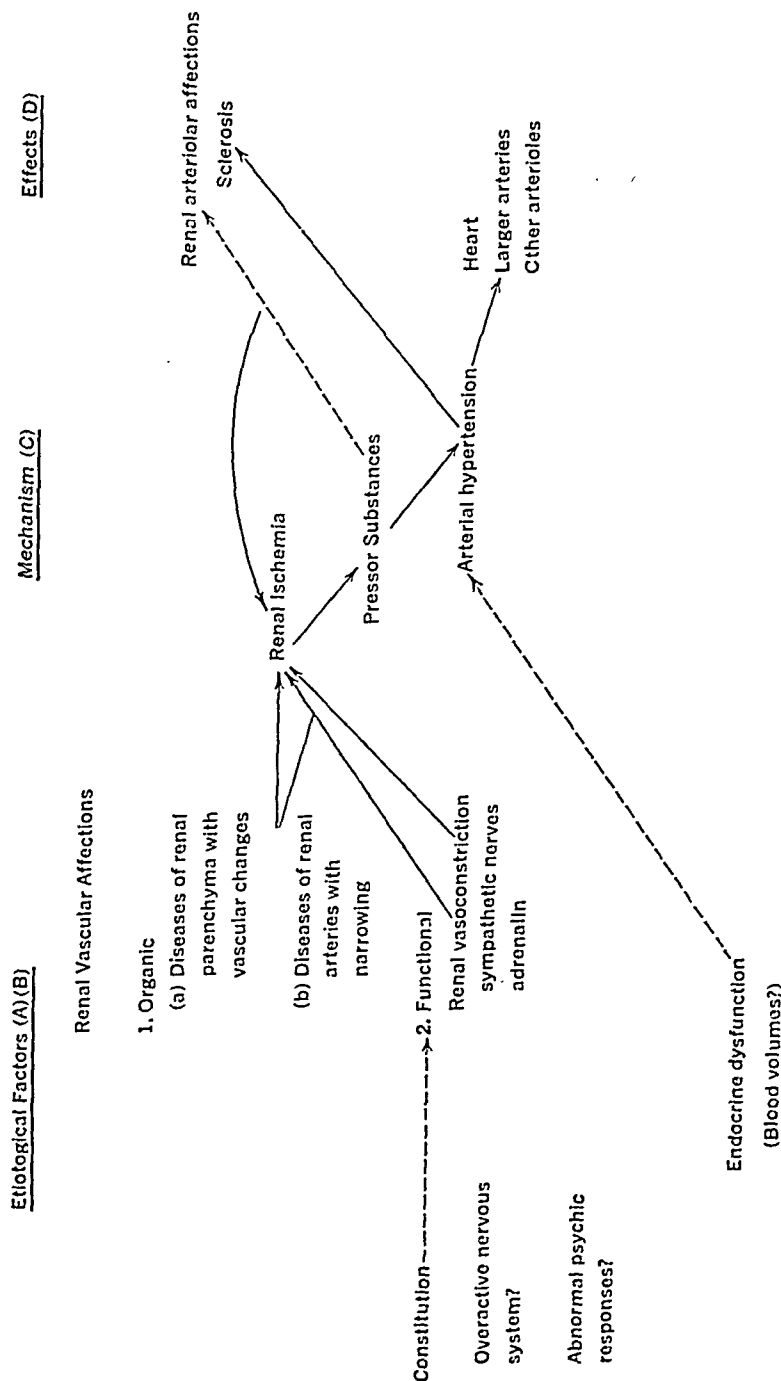


FIG. 1.—A concept of the mechanism of arterial hypertension. The letters A to D refer to paragraphs in the text. Taken individually those arrows marked by a solid line represent influences which have been demonstrated in experiments or by other good evidence; those marked by a dotted line are less well understood. Briefly, in predisposed individuals renal ischemia can be caused by intermittent functional renal vasoconstriction, by this in conjunction with organic narrowing of the renal vascular system, or (rarely) by the latter acting alone. The resulting hypertension causes organic changes in the renal arterioles which continue the existence of ischemia and hypertension.

either obviously high-strung, emotional, excitable people, or they admit the occurrence of great internal excitement which they manage to keep under control. Their responses to ordinary emotional stimuli are often excessive.

Third, organic renal diseases seem to cause hypertension in certain individuals^{20,28,38} and not in others. These facts suggest that some persons are more susceptible.

The "constitutional component" means, therefore, a defect in certain individuals which predisposes them to arterial hypertension. This defect may be hereditary, or the result of early environmental influences. Its obvious clinical manifestations refer to the nervous system, especially to those structures having to do with emotional reactions and their effects upon blood-vessels. That the sympathetic nervous system may exert a pronounced effect upon the blood-vessels of the kidneys is discussed elsewhere.

Animals also exhibit different degrees of susceptibility. In most dogs, *both* renal arteries must be constricted in order to induce chronic hypertension,¹⁰ although occasionally they develop it after constriction of only one. (This applies particularly to excitable, nervous dogs. Three such animals in this laboratory exhibited arterial hypertension for 18 months after 1 kidney was treated.) Rats, on the other hand, are affected by injury to 1 kidney,^{46*} developing cardiac hypertrophy and hypertension^{33,36} often with renal arteriolar necrosis.

B. The Causes of Renal Ischemia. 1. ISCHEMIA DUE TO ORGANIC VASCULAR CHANGES. (a) *Diseases of the Smaller Blood-vessels.* In *man* the persistence of hydronephrosis results in marked diminution of the vascular supply of the kidney and so probably leads to renal ischemia.⁷ It is probable that chronic atrophic pyelonephritis also results in ischemia, scarring of the parenchyma after infection has healed producing lesions of blood-vessels resulting in reduction of blood flow.^{6,45} The effects of renal infections upon blood flow have been little studied. Lesions resulting from chronic glomerulonephritis found postmortem suggest, from the pathologic viewpoint, that renal ischemia may have been present. Renal ptosis may be accompanied by ischemia.²¹ Trauma results in a similar change especially if scarring follows. Other renal diseases may produce similar effects.

In *animals* obstruction to the flow of urine during brief experiments results in renal ischemia;⁸ in rabbits, profound vascular changes accompany protracted experiments.¹⁸ Many other affections of the kidneys experimentally produced can be regarded as resulting in ischemia.

Arterial hypertension is often associated with renal affections in *man*: with pyelonephritis,⁴⁵ nephroptosis,²¹ prostate obstruction,²⁴

* Attempts to produce hypertension by causing unilateral hydronephrosis, while successful in rats, failed in dogs.

hydronephrosis, and many other abnormalities of the kidneys.^{20,28,38} Indeed, certain individuals develop elevated blood pressures as an early accompaniment of Bright's disease resembling cases of "essential hypertension."⁹

In *animals* arterial hypertension accompanies many of these conditions when they are experimentally produced. In rats it occurs with considerable frequency when one kidney is affected by perinephritis induced by cellophane,²⁵ traumatic injury and hydro-nephrosis.^{33,36} In rabbits and dogs other renal affections, probably resulting in ischemia, appear also to cause it.

It is not certain whether a single lesion of the renal arterioles, arteriolar sclerosis, causes or results from arterial hypertension in man. Because the evidence in animals suggests, however, that it follows elevation of blood pressure, it is in this case regarded as an *effect* of the disease. This relation is discussed elsewhere.

(b) *Diseases of the Larger Arteries.* Narrowing of the mouths of the renal arteries by arteriosclerotic changes appears to reduce renal blood flow in a manner analogous to the principle of the Goldblatt clamp, as does narrowing of their lumina at their bifurcation, or in their intrarenal branches. The degree of ischemia, and the amount of renal tissue which is ischemic depends, of course, upon the location and extent of the lesion. Other more unusual affections of the arteries supplying the kidneys also cause ischemia, such as progressive thrombosis of the aorta, periarteritis nodosa, and perhaps coarctation of the aorta.

In *animals*, partial constriction of the renal artery obviously causes renal ischemia.¹⁰ Partial constriction of the aorta above the mouths of the renal arteries brings about the same result.^{31,43} These procedures lead to general vaso-constriction and arterial hypertension and to a change in intrarenal hemodynamics constricting the efferent arterioles.⁵

Arterial hypertension has been related to renal arteriosclerosis,¹ to periarteritis nodosa and to coarctation of the aorta.^{31,43} All are believed to be dependent on ischemia.

2. ISCHEMIA DUE TO FUNCTIONAL DISTURBANCES. Injection of adrenalin into *human beings* results in prolonged renal vasoconstriction more especially of the efferent arterioles.⁴⁰ Psychic stimulation (anxiety) also can apparently produce renal ischemia.⁴⁰ This effect is achieved either through the liberation of adrenalin or through activity of the renal vasoconstrictor nerves of the sympathetic nervous system.

In *animals*, injection of adrenalin produces renal ischemia, the efferent arterioles being affected by small doses and the afferent also by larger ones.³⁰ Stimulation of the renal sympathetic nerves causes the same effect.³

Prolonged arterial hypertension has not been produced experimentally by either of these means. In rats the injection of single

large doses of adrenalin leads to cardiac hypertrophy.^{33,36} Transient hypertension (4 to 6 weeks) may follow the injection of adrenalin in oil in dogs with normal blood pressures when one kidney is ischemic.⁴⁴

In *human beings*, the sympathetic nerves supplying the splanchnic area are extremely important in maintaining an elevated blood pressure. When all of them are cut by means of preganglionic resection⁴¹ (thus effectively denervating the kidneys), arterial hypertension and its effects disappear in a large proportion of cases. Because renal blood flow is not always reduced by this procedure, but sometimes increases,⁴² these nerves probably exert an adverse influence upon it, contributing to hypertension by the results of their action. The possibility, therefore, exists that repeated psychic stimulation in predisposed individuals, by affecting the renal sympathetic nerves, results in enough renal ischemia to cause hypertension. If stimulation continues long enough, hypertension would become permanent from the establishment of changes in the renal arterioles.

3. THE RELATION BETWEEN ORGANIC AND FUNCTIONAL RENAL ISCHEMIA. In anesthetized dogs when ischemia results from partial constriction of the renal artery, it is profoundly influenced by the injection of adrenalin.³⁹ Moderate reduction in renal blood flow of short duration results from large doses if the kidney is normal; if a mechanical clamp has been applied to a renal artery and blood flow has already been reduced, minute doses produce greater effects lasting much longer. When the kidney is already ischemic the action therefore is markedly increased.

Arterial hypertension may result, furthermore, from the summation of these two actions (adrenalin and constriction), although neither of them alone has had much effect. Chromaffin tissue or the sympathetic nervous system may, therefore, play a part in the production and maintenance of hypertension by the Goldblatt method. This possibility has not been investigated in man.

C. The Mechanism of Hypertension Due to Renal Ischemia. When kidneys are ischemic, pressor substances enter the general circulation. These act on the smooth muscle of arterioles, increase peripheral resistance and, therefore, raise blood pressure. The nature of this material and the manner of its coming into existence is uncertain.

There are two principal theories: Page²⁶ believes that renin is released by kidneys when their pulse pressure is reduced. Renin, he thinks, then acts upon a pseudo-globulin in the blood to form "angiotonin," which has been isolated and identified as a pressor substance. It is the action upon arterioles of angiotonin, or products arising from it, that causes hypertension. As a variant, another group of investigators²³ regards renin as an enzyme, which acts upon its globulin substrate to form a pressor substance "hypertensin"

(identical with "angiotonin"). Another enzyme, "hypertensinase," present in blood and tissues, destroys it.

The second view is that of Holtz.¹⁹ Kidneys contain the enzymes decarboxylase and amine oxidase, the latter acting only in the presence of oxygen. When the supply of oxygen is reduced (*i. e.*, during ischemia), decarboxylation of certain amino acids continues, but deamination is incomplete. The partial interruption of the metabolism of these amino acids results in the formation of amines, many of which are pressor substances. The most powerful are phenolic compounds.* Amine oxidase has a certain specificity; it catalyzes the oxidation only of compounds having an amino group on the end of a side chain,² and does not affect diamines. Its action is much greater on amines containing a phenolic nucleus (tyramine and its derivatives, indolethylamine).

D. The Effects of Hypertension on the Vascular System. Chronic arterial hypertension produces certain effects on the heart, blood-vessels and kidneys. The heart becomes enlarged and the wall of the left ventricle thickened. This change is greater when the coronary arteries are affected.

When the level of blood pressure is very high (in younger individuals), or when general arteriosclerosis accompanies hypertension, arteries may rupture. The consequences are important if the ruptured vessel is in the brain. In other localities less serious disturbances result.

The nature of the effect of arterial hypertension on the vessels of the kidneys is less clear. Sclerosis of the afferent arterioles is an almost universal accompaniment of chronically elevated blood pressure.²² Constriction of the efferent arterioles, and of course renal ischemia, is present in most cases.^{11†} It is not yet certain whether arteriolar sclerosis comes first and then ischemia and hypertension, or hypertension causes changes in the arterioles which then serve to make permanent narrowing of the renal vascular bed.

There is some evidence for the relation of these occurrences in experiments. In rats, when hypertension results from injury to one kidney, arteriolar sclerosis (and necrosis) are found in the other.^{33,36,46} Dogs develop these lesions in organs other than the kidneys when bilateral renal ischemia is marked.¹⁰ In human beings exhibiting one diseased kidney, nephrectomy reduces blood pressure when renal vascular disease is not advanced.³⁵ These observations suggest that renal arteriolar sclerosis accompanies hypertension,

* Because angiotonin is inactivated by tyrosinase³⁴ it is probably a phenolic compound.

† It is interesting in this connection that the efferent arterioles are constricted by many of the influences believed to be implicated in arterial hypertension; adrenalin and related compounds, renin and angiotonin, the action of the sympathetic nervous system. A situation exists in the kidneys, therefore, which may not only cause hypertension, but also be an effect of it.

and is one of its effects. The lesions then prevent the reestablishment of normal blood flow.

Endocrine Dysfunction and Hypertension. The nature of what has been called "endocrine" hypertension is less clear. In rats, Byrom⁴ produced in the livers and kidneys vascular lesions similar to those seen in eclampsia, by injecting pitressin after previous administration of female sex hormone. Griffith¹² has induced arterial hypertension in them by the use of posterior pituitary extract and water. He has also suggested that hypertension may result from retention of water and increase in the circulating volume of blood.¹³

In *human beings*, some hypertensive individuals have in their plasma antidiuretic substance; a few have been improved by irradiation of the pituitary gland with Roentgen ray.²⁹ Fall in the level of blood pressure along with disappearance of the antidiuretic substance suggests a relation between them.

The association of some cases with endocrine diseases is well established. If endocrine dysfunction is the initiating factor, the maintenance of the disease may be dependent on secondary renal arteriolar changes.

Recapitulation. Arterial hypertension, according to this idea, is therefore a state characterized by increased peripheral resistance owing to the presence of circulating pressor substances in the blood. These substances are released by ischemic kidneys and may be of several varieties.⁴⁷ They cause changes in arterioles, and in the hemodynamics of the kidneys, leading to arteriolar affections. A "vicious circle" is therefore established: renal ischemia giving rise to hypertension, which results in renal arteriolar sclerosis and the maintenance of ischemia (and hypertension).

Two conditions which occasion renal ischemia, therefore, initiate this "vicious circle:" 1, functional (spasmodic) constriction of arterioles by nervous or hormonal influences; and 2, structural (organic) changes in the renal blood-vessels. A third condition, also a structural change (renal arteriolar sclerosis) arises as a result of hypertension, acting in such a way as to continue the existence of renal ischemia. The first is probably active in most cases of hypertension,* varying considerably in degree in different individuals, but capable of initiating it alone under the proper circumstances. When organic renal ischemia is already present, hypertension may result from slight intermittent increase in renal vasoconstrictor tone. When the kidneys are otherwise normal, the activity of the sympathetic nerves must be comparatively greater, and their action called into play repeatedly in order to initiate the sequence of events leading to chronic hypertension.

Discussion. The view here presented makes clear some of the variations of the disease arterial hypertension. It usually depends upon two factors (rarely one) which cause a third, a similar one, to

* This may not be true for the hypertension associated with renal insufficiency.

come into being. Obviously the rate of progress of the condition resulting from these factors is determined by the relative parts which each play.

If the functional element acts alone, the course of the disease is prolonged (benign), depending for the most part upon the degree and frequency of action of the renal vaso-constrictor nerves, and those factors which influence them. Patients exhibiting symptoms predominantly of nervous origin vary, therefore, in their courses from long-standing "mild" hypertension, to a severe disease characterized by a labile blood pressure easily influenced by rest and sedatives. Rarely does the course become "malignant."³⁷

If the structural element is progressive, and the functional one continues to exert its influence, the course of the disease is more rapid and death results from renal insufficiency.³⁸ On the other hand, if the structural element is stationary or only slowly progressive (as in arteriosclerosis), the course depends upon the influence of the functional element. If both the functional and structural elements act with increasingly greater influence, a "malignant" course results. (Although, as some think, the so-called "malignant" hypertension may be a distinct disease with a distinct pathologic anatomy, as indicated by the term, necrotizing arteriolitis, on clinical grounds it often appears to be a terminal stage of chronic arterial hypertension.) Other cardiovascular conditions also affect the outcome.

Procedures designed to alter these influences, and therefore the disease itself, naturally fall into three classes. A. The functional (spasmodic) factor can be changed by removing those environmental influences which cause constriction of the renal blood-vessels, by the administration of sedatives to lessen their effects, by the reëducation of the individual so that he no longer reacts to them, and by the surgical interruption of the effector pathways of the sympathetic nerves supplying the kidneys. B. The structural (organic) factor can be altered by the removal, for example, of a diseased, ischemic kidney, by attempting to influence degenerative vascular affections of the kidneys, or by increasing renal blood supply through surgical methods. C. The pressor substances responsible for hypertension can perhaps be destroyed by some of the newer extracts, thereby preventing the *effects* of the disease from progressing. Obviously the value of any of these methods depends for the most part upon the degree of secondary arteriolar sclerosis present in kidneys subjected to long-standing arterial hypertension.

Summary. A way of thinking about arterial hypertension has been presented, which takes into account the possible rôle of renal ischemia and those factors which cause it.

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BOOK REVIEWS AND NOTICES

CLINICS. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Successor to *The New International Clinics*. Philadelphia, J. B. Lippincott Company. Bi-monthly publication. Price, \$12.00 a year.

After 4 years, *The New International Clinics* has given way to the present journal, which aims to acquire flexibility by selecting material on the basis of its practical significance, rather than as coming from special institutions or localities. The new journal will appear every 2 months, supplemented by original articles, brief "clinics," and occasional Reviews of recent progress. The Editorial Board shows but little change, the retention of Dr. John W. McNee and Dr. Jonathan C. Meakins preserving its international character. The first number is a symposium on Burns and Shock, and includes 6 articles.

E. K.

PHARMACOPŒIA OF THE UNITED STATES OF AMERICA. Twelfth Revision.

By authority of the U. S. Pharmacopœial Convention meeting at Washington, D. C., 1940. Prepared by the Committee of Revision and Published by the Board of Trustees. Pp. 880. Easton, Pa.: Mack Printing Company, 1942. Price, \$7.50.

Our Pharmacopœia needs no recommendation. The modifications of this 12th decennial revision and of future plans are best seen in the following quotations from the Preface:

"Certain basic policies were written into the first Pharmacopœia in 1820, and the Twelfth Revision marks a new era in its growth and development. For the first time a program is fully launched for a new Pharmacopœia every five years, a bound 'supplement' halfway between, and, to meet the frequently occurring situations which require immediate attention, 'Interim Revision Announcements' or sheet 'Supplements,' whenever these are required. By these accelerated procedures the Pharmacopœia is endeavoring to keep pace with the rapid developments of modern medicine and the related sciences. . . .

"Dr. Lyman Spalding, the founder and Chairman of the first United States Pharmacopœia, stated 'It is the object of a Pharmacopœia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood.' Advisory boards and committees have been authorized for collaboration in the standardization of many U.S.P. products. These items include the vitamins, anti-anemia preparation, sterile products for parenteral use and for the needs of surgery, blood substitutes, glass container standardization, the assay of digitalis, ergot, parathyroid, epinephrine, insulin, adrenal cortical extract, the sex hormones, and numerous other substances and tests. . . .

"Since the publication of the U.S.P. XI, the revised Federal Food, Drug, and Cosmetic Act of 1938 has been enacted by Congress, and the Pharmacopœia of the U. S. is recognized as one of the 'official compendia.' The officials of the Canadian Government have collaborated in the preparation of some of the U.S.P. standards. There has also been close co-operation between the British Pharmacopœial Commission and the Committee of Revision of the U.S.P. The co-operation of the U.S.P. Auxiliary Commissions of Cuba and Puerto Rico and the Pan American Sanitary Bureau officials at Washington and also the U.S.P. Auxiliary Commission of the Philippines has materially assisted in extending the information carried by the U.S.P. into many other associated countries. . . .

"To assist in extending information both to physicians and pharmacists concerning the scope, therapeutic value, and use of pharmacopœial drugs and preparations, 48 articles were prepared under the supervision of a special Committee of the Pharmacopœia and officers of the American Medical Association. The authors of these articles were selected because of their special knowledge of and experience in the medical problem under consideration. . . ."

Our Therapeutic Progress department contains two valuable discussions of the Revision (May, 1942 and this number).

SYNOPSIS OF ANO-RECTAL DISEASES. By LOUIS J. HIRSCHMAN, Professor of Proctology, Wayne University. Second Edition. Pp. 315; 182 illustrations and 12 color plates. St. Louis: C. V. Mosby Company, 1942. Price, \$4.50.

THE Synopsis has been revised and some new material added. The local use of sulfanilamide is recommended in connection with some of the surgical procedures. A chapter has been added on Focal Infection of Ano-rectal Origin in which it is suggested that certain patients be desensitized to selected bacteria recovered from the anal crypts by hypodermic injections of 2 to 25 organisms at intervals of 5 to 7 days. Lymphopathia venereum is not indexed. The volume should be of value to the many readers who found the first edition useful.

J. R.

THE RECEPTION OF WILLIAM BEAUMONT'S DISCOVERY IN EUROPE. By GEORGE ROSEN, M.D. Foreword by JOHN F. FULTON, M.D. Pp. 97; frontispiece of William Beaumont. New York: Schuman's, 1941. Price, \$5.00.

BEAUMONT's famous observations on the digestive activities of St. Martin's exposed stomach and his equally famous book—destined in Claude Bernard's words, "to produce an epochmaking effect in the history of digestion"—are properly cherished by the present generation as one of the greatest glories of American medicine. The little book is a bibliophile's *rarissima*, only recently reprinted again, and the man has been honored repeatedly with biographies, medals, shrines and lectureships. Little attempt seems to have been made, however, to trace the recognition of the book and of Beaumont's achievement in the century that has since elapsed.

This carefully prepared study by Dr. Rosen satisfactorily fills the gap. Even ardent Beaumontophiles may be surprised to learn of the quickly favorable response abroad: the German, English and French articles, for instance, that appeared even before the publication of the "Experiments & Observations" in 1833; the prompt and favorable discussions of the new book in 1834 and 1835; foreign editions and translations; recognition by Claude Bernard and Carl Ludwig. Equally surprising is "the fact that during the last 40 years of the century Beaumont's researches are only mentioned three times," attributed by Dr. Rosen to Kussmaul's introduction of the stomach pump in 1867, and to greater emphasis on the chemical aspects of digestion.

Among items that might be objected to, though they are to be sure insignificant in evaluating the booklet, are: the many "incomplete" references, the omission of J. R. Young's "Experimental Inquiry" in the chapter on "Gastric Physiology before Beaumont" and Dr. Fulton's foreword limitation of Americans who profoundly influenced European medical thought before 1900 to Beaumont, Franklin and Weir Mitchell. Granted the flexibility of "profoundly," many would feel that Long and Morton, McDowell and Marion Sims, Gorgas, John Shaw Billings, and perhaps still others, might well be admitted to this august company.

E. K.

HISTORY OF THE SCHOOL OF NURSING OF THE PRESBYTERIAN HOSPITAL. By ELEANOR LEE, A.B., R.N., Assistant Professor of Nursing, Department of Nursing, College of Physicians and Surgeons, Columbia University. Pp. 286; 58 illustrations. New York: G. P. Putnam's Sons, 1942. Price, \$3.50.

THIS book covers far more than its title indicates, as one is very soon aware on reading this fascinating account of the development of this School of Nursing.

In the background one sees the picture of the community that New York was in 1892 with its poor that provided the need out of which grew a service built up by men and women from the citizens, who were socially minded, as well as those devoted members of the medical and nursing fields without whose loyal and constant attention such a fine institution could not have occurred.

With letters, pictures and diaries one gets a most intimate impression of how the present organization came about. It represents what was happening in many places throughout the whole country, a gradually emerging social conscience, an awakening to the needs of the underprivileged and of the responsibility of those in possession of scientific knowledge to meet those needs.

One might take as a prediction of the future social importance of nursing, the last sentence in the Appendix, which reads: "The nurse of this era who keeps pace with the advance of science will have undreamed-of opportunities to contribute to the betterment of the mental and physical health of mankind."

This book should be interesting to all who are engaged in the medical professions or who are aiding in any way the progress of this great work.

M. S.

DR. BARD OF HYDE PARK. By J. BRETT LANGSTAFF. With an Introduction by NICHOLAS MURRAY BUTLER. Pp. 365; 12 illustrations. New York: E. P. Dutton & Co., 1942. Price, \$3.75.

DR. SAMUEL BARD is the famous physician who saved George Washington's life, when shortly after his inauguration Dr. Bard removed an anthrax carbuncle on his thigh. Dr. Bard was a founder of the Medical School in King's College, now the famous College of Physicians and Surgeons of Columbia University. These, perhaps may be counted as the most noted of his achievements, for the great works of man live after him. But they were only a part of the rich and full life of this remarkable man.

It is evident from the very beginning of the book that the author has spent many years in careful research on his subject. The reader may feel at times as if the research was the more important part of the biography, yet the vigorous personalities of Dr. Samuel Bard and of his father, Dr. John Bard, hurdle the dry facts which might otherwise weigh them down. Both father and son lived well into their 70's—one cannot write of the son without talking of the father, for each was so close to the other—and their lives were rich, full and vigorous to the end.

Dr. John Bard, the father, inherited from his wife's side of the family the Hyde Park property that is now the site of the home of our present President. Thus are linked the doughty characters of Revolutionary times with our present day historical figures, and dead names become living people.

This book presents, as fully as is possible in a popular biography, the complete and interesting life of Dr. Samuel Bard and also a small part of the Bard family background. As Samuel was an American of the third generation, his grandfather having come to America because of Huguenot persecutions in France, a feeling of liberty and sympathy for all people

predestined the character of Samuel Bard. His untiring search to relieve pain was the most natural of careers that he could follow, for the father Dr. John Bard, did much to crystallize his son's ideals. How well these foundations were laid is evidenced by the fact that Ducachet, his colleague, said: "There never was a medical man in the City of New York so universally known, so much beloved and esteemed as a practitioner. Indeed, so astonishingly popular was he at one time that notwithstanding the number of worthies who flourished contemporaneously in the same city, he was called to almost every person who was taken sick." E. F.

CLINICAL CARDIOLOGY. By WILLIAM DRESSLER, M.D., Attending Cardiologist, Israel Zion Hospital; Assistant Attending Physician, Brooklyn Hospital, New York. Pp. 692; 108 illustrations. New York and London: Paul B. Hoeber, Inc., 1942.

THE author states that the aim of this volume is to offer a practical guide to those who wish to engage in the study of heart disease and that particular emphasis has been placed on the use of inspection, palpation, percussion and auscultation. The entire field of clinical cardiology, including hypertension, is discussed. There are brief chapters on electrocardiography and roentgenologic examination. The book is concluded by a list of 294 statements, covering nearly 40 pages, entitled "Important Points to Remember."

After comparing this book with 4 of its recently published competitors in the same field, this Reviewer is unable to rank the present volume high in the group despite the fact that it contains much of the same orthodox material found in the others. Occasionally major errors are found, such as the statement to the effect that the intervals between all three sounds in gallop rhythm are practically equal. It is interesting that the author's conception of electrical potential is such that he can speak of potential differences having various directions. Opinions, some of which do not seem to be supported by the weight of available evidence, are at times stated so dogmatically in this book that the uninitiated would have no reason to suspect that they are opinions. Finally a statement that "... it has become almost a routine procedure to prescribe digitalis whenever a heart disease, or merely an innocent murmur has been detected" suggests that the author has a much worse opinion of the standards of American practitioners than some who have worked with them for a much longer time. The book is not recommended. C. W.

QUESTIONS IN LABORATORY METHODS. By R. B. H. GRADWOHL, M.D., Director of the Graduate School of Laboratory Technique, St. Louis, Mo. Second Edition. Pp. 71. St. Louis, Mo.: The Gradwohl School of Laboratory Technique, 1942. Price, \$2.50.

THIS is a well-printed 71-page booklet bound with spiral wire and heavy paper cover, measuring approximately 8 x 11 x $\frac{1}{4}$ inches. It is a compilation of "questions . . . taken from examination papers . . . accumulated over a period of 25 years" sorted as follows: The Microscope (255 questions), Metric System (86), Clinical Microscopy (318), Hematology (1647), Bacteriology (1589), Serology (117), Clinical Chemistry (275), Parasitology (204), Histological Technique (163), Basal Metabolism (45), Special Tests (191), and Miscellaneous Medical Subjects (345); a total of 5235 questions. This is the only publication of its kind in this field at present so far as the Reviewer is aware.

There are many questions in every section which, in the opinion of the

Reviewer, should not be put to laboratory technicians. These deal with diagnostic implications of laboratory findings, and are outside the proper province of the technician. They might be helpful to the physician preparing for special examinations.

D. B.

PSYCHOSURGERY. By WALTER FREEMAN, M.D., PH.D., and JAMES W. WATTS, M.D., with THELMA HUNT, M.D., PH.D. Pp. 337; 81 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$6.00.

FREEMAN and Watts, who have pioneered in the neurosurgical treatment in Psychiatry, have prepared a valuable survey of the history, the neuro-anatomy, the physiology and the technique of prefrontal lobotomy and have reviewed the results of their own operations in psychotic patients and the available literature and presented it in a well-organized and scientific evaluation.

In Part II, entitled "The Frontal Lobes," the historical concepts, anthropology, topographic anatomy, the connections and functions of the frontal lobes are all adequately reviewed and material derived from experimental animals, the symptoms of frontal lobe tumors, frontal lobe atrophy, softenings and injuries and the results of frontal lobotomy in man are reviewed and evaluated in relation to the therapeutic surgical procedure.

Part III relates to clinical observations of prefrontal lobotomy and describes the improvements made by Freeman and Watts on the original Moniz technique.

There is a chapter devoted to the functions of the frontal lobes, a chapter on Mental Mechanisms and the Frontal Lobes which the critical reader will evaluate (as Drs. Freeman and Watts suggest) according to his own judgment. Some of the alterations in the mental functions reported and discussed are: 1, Reduced capacity of an individual to project himself into the future. 2, Restraint is somewhat impaired. 3, Reduced self-critical and self-absorptive capacity. 4, More extraverted, freer conduct. 5, Vivid but superficial emotional responses. 6, Delusional ideas may be retained but unpleasant emotional reaction to them is absent. 7, Impaired foresight.

The postoperative reëducation and rehabilitation of patients subjected to frontal lobotomy are of the utmost importance. Possibly this phase of treatment could be emphasized and outlined in greater detail in the book. Freeman and Watts have been very frank in assaying the positive and negative elements in frontal lobotomy and give a very fair statement as to the immediate as well as the ultimate risks. The operation is a drastic, last resort method and should be used only in those long-standing cases which fail to respond to other methods. Probably like other drastic treatment methods in Psychiatry, its development and application were stimulated by the demand for more direct treatment of the large static segment of the psychoses. It must be understood that recovery cannot be anticipated in patients subjected to frontal lobotomy. While one of the remarkable features of the operation is lack of apparent intellectual defect, it must not be stated that some defect of intellectual-emotional functions do not result. Throughout the book there is a frank approach to the question of accomplishment by the operation and there is no dodging of the issue regarding the unfavorable consequences.

The book is factual, well written, profusely illustrated with well-chosen photographs and drawings and charts. The psychiatrist will find the text fascinating, a valuable addition to his library and the neurosurgeon will be accurately informed as to technical detail. The volume offers an extension of knowledge for the psychologist, sociologist and every student of human emotion and conduct.

H. P.

THE CARE OF THE AGED (GERIATRICS). By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Department of Public Health. Fourth Edition. Pp. 589; 50 illustrations. St. Louis, C. V. Mosby Company, 1942. Price, \$7.00.

THE first edition of this work appeared in 1919, the third not until 1936. Because of the recent remarkable increases in the average duration of human life and the keener interest in the subject of geriatrics, a fourth edition is required after 6 years. The rôle to be played by the aged in our total war effort has also become an important matter, and still more so is the problem of those in whom old age can be deferred.

The need for books of this kind, then, is obvious. The ability to condense adequate information on the subject into less than 600 small pages is at once questioned, and perusal confirms the opinion that a book half as long again would be twice as valuable. The leukemias in 2 pages, the eye in 6 pages, the ear in 7, could hardly get adequate attention.

Nevertheless, the book is well worth while, and as each edition has been an improvement on its predecessor, let us hope that a greatly enlarged fifth edition will soon appear. E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 26, No. 4, July, 1942. Symposium on Industrial Medicine. Pp. 1345. Philadelphia: W. B. Saunders Company, 1942.

CONTENTS: "The Physician in Industry," by Dr. Carl M. Peterson; "Organization and Management of Industrial Medical Service," by Dr. A. L. Brooks; "Prevention of Ill Health in Industry," by Dr. Grant L. Bird; "Workmen's Compensation and Medicine," by Dr. Raymond Hussey; "Tuberculosis as a Compensation Problem," by Dr. C. O. Sappington; "Nutrition in Industry," by Dr. William A. Sawyer; "A War-Survey of Industrial Psychiatry," by Dr. Lydia G. Giberson; "The Measurement of Sickness Among Industrial Workers," by Dr. William M. Gafafer; "Fatigue and War Production," by Dr. Robert H. Flinn; "Prevention of Ill Health in Industry," by Dr. John H. Foulger; "Methods Employed in the Appraisal and Control of Industrial Health Hazards," by J. J. Bloomfield; "Indoor Environmental Atmosphere and Its Control," by Dr. W. J. McConnell; "Protective Ointments and Industrial Cleansers," by Dr. Louis Schwartz; "Effects of High Pressures; Prevention and Treatment of Compressed Air Illness," by Dr. Albert R. Behnke, Jr.; "The Pneumoconioses," by Dr. L. U. Gardner; "Lead Absorption and Lead Poisoning," by Dr. Robert A. Kehoe; "The Toxic Properties of Selected Less Familiar Metals," by Drs. Carey P. McCord and John J. Prendergast; "Recent Progress in Aviation Medicine," by Dr. Benjamin F. Jones.

Seldom has a publication concerned with industrial medicine held so much practical information in such a small space, as does the "Symposium on Industrial Medicine." The field in this branch of medicine is as varied and wide as the industry which it serves, yet nearly all phases are represented with a precise brevity by physicians who are recognized authorities.

The book can be read in 6 hours by an alert student but it lends itself well to broken reading. The usefulness of the volume is not restricted to those specializing in industrial medicine, and it should prove of particular value to physicians in these crowded days, who are being asked to include medical work in industrial plants that have been created for or converted to war

products in the past few months. In many instances this work is just as new to the physician as the plant is to the managers and workers, and there should be an especial thanksgiving that the publishers have filled the need for a clear discussion of industrial medical problems at this time.

V. R.

THE SURGERY OF PANCREATIC TUMORS. By ALEXANDER BRUNSCHWIG, M.S., M.D., F.A.C.S., Professor of Surgery, University of Chicago. Pp. 421; 123 illustrations, 1 color plate. St. Louis: C. V. Mosby Company, 1942. Price, \$7.50.

INTEREST in the surgery of the pancreas has greatly increased in recent years, due to the recognition of island adenomas as a cause of hyperinsulinism and to the development of successful methods of attacking carcinoma of the head of the pancreas. Dr. Brunschwig has been a pioneer in this work and his monograph is the most thorough and complete treatise that has appeared on the subject. It should be available to every surgeon who contemplates the removal of pancreatic tumors and its perusal by physicians generally should lead to a clearer recognition of the possibilities and limitations of pancreatic surgery.

J. R.

ELECTROTHERAPY AND LIGHT THERAPY with the Essentials of Hydrotherapy and Mechanotherapy. By RICHARD KOVÁCS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and West Side Hospitals. Pp. 735; 413 engravings and a color plate. Fourth Edition. Cloth. Philadelphia: Lea & Febiger, 1942. Price, \$8.00.

SINCE this well-known work first appeared some 10 years ago the rapid progress in physical therapy and the great demand for the book have necessitated new editions of which the present one is the fourth.

As in the previous editions, so also in this one, the subject matter is well organized. It begins with the essential physics—avoiding formulas and complicated equations—of electrical and light energies. Then follow in succession detailed descriptions of the various devices for the production of these energies, their physical and physiologic effects, indications and contraindications, technique of administration and their possible dangers. One new feature of this edition is the incorporation of 3 rather sketchy chapters on hydrotherapy and mechanotherapy. Next there follows a description of the application of physical therapy in a great variety of diseases and disorders in the various branches of medicine. This latter part of the book has been considerably enlarged, covering nearly one-third (217 pages) of the text. Discussion of treatment by means of various electrical and light agents naturally predominates in this part of the book, but, as the author states, "the correlated or interchangeable use of other and often simpler physical measures have always been emphasized." Several electrodiagnostic charts and tables have been appended to the text. A well-selected bibliography appears at the end of each chapter.

The relation of electrodiagnosis to the newer electrophysiology has been further stressed and new chapters have been devoted to short wave diathermy. The electric shock therapy method in mental conditions has been thoroughly described and chapters on peripheral vascular disease, chronic arthritis, traumatic and skin conditions rewritten and amplified.

Like the earlier editions, this book is an authoritative, comprehensive exposition of electro and light therapy. In reading the text, one is impressed with the author's thorough knowledge of his subject and his ability

to present the material in a clear, instructive manner. Relatively little space has been given to the discussion of controversial matters and to theories of a purely academic interest, the volume having been devoted chiefly to the description of methods of established value and to the discussion of problems of practical importance. In its field this book is a standard work in which the admirable text of the previous editions has been amplified and revised to include the latest developments in the field. This work cannot be recommended too highly.

J. N.

STANDARD NOMENCLATURE OF DISEASE AND STANDARD NOMENCLATURE OF OPERATIONS. Edited by EDWIN P. JORDAN, M.D. Third edition. Pp. 1022. Chicago: American Medical Association, 1942.

It is hard to understand why this authoritative Standard Nomenclature of Disease has not come into more general use since its compilation in 1933 by a distinguished group of medical men under the auspices of the Commonwealth Fund. The present "completely revised" edition has been developed under new auspices with a new editor and editorial advisory board; but retains the same basic plan and arrangement. Based on the Dewey decimal system, a Topographical Classification (to three digits) presents the parts of the body in 11 main divisions. An Etiological Classification in 12 main divisions covers all known causes of disease. Thus, ankylosis of the knee (tuberculous) would be numbered 248-123.4 (2, muscular-skeletal system; 4, a joint; 8, knee-1, infection; 2, a lower organism; 3, tubercle bacillus; .4, the result—ankylosis).

The commoner diseases have been picked out in bold-face type, and a standard classification of operative procedures added. The Introduction and Instructions to Librarians aid the beginner to overcome rapidly the superficially formidable arrangement. Various small additions have been made and the new edition is more easily usable by the beginner. We intend to make regular use of the classification in our own work and are sure that such a course would be desirable in all hospitals and other centers concerned with scientific medicine.

E. K.

DEMONSTRATION OF PHYSICAL SIGNS IN CLINICAL SURGERY. By HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London, etc. Eighth edition, revised. Pp. 336; 455 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$7.00.

This book is designed primarily for medical students and house officers but it is well worth the consideration and time of many surgeons who have finished their training. It contains a concise review of the physical signs which may be elicited in various surgical conditions and emphasizes important points to be sought in the history in connection with them. The methods of eliciting these signs are well illustrated. Many of the plates are in color. The evaluation of their significance is helpful when given in terms of the author's own experience.

No two surgeons are likely to agree completely on the evaluation of physical signs and students of this book may subsequently revise the importance of certain signs in the light of their own experience. However, the value of the book lies in emphasizing physical signs which are not elicited as frequently as they should be, and in demonstration the great amount of information which can be obtained without resort to complicated and time-consuming laboratory procedures.

J. R.

ARCHITECTURAL PRINCIPLES IN ARTHRODESIS. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Pp. 132; 144 figures. St. Louis: The Williams & Wilkins Company, 1942. Price, \$7.50.

WELL done, indeed! This splendid treatise on the architectural principles in arthrodeses is a genuine contribution to bone surgery. The principles, so well developed, so carefully portrayed, are by no means restricted to arthrodeses alone, but apply to bone repair in general.

From the foreword by Harry Platt, to and including the last chapter, one is impressed with the deep thought and reflection given to the entire subject.

The indications for an arthrodesis are generally accepted and may be regarded as uniformly sound. The common causes of failure are enumerated and the mechanical basis for their occurrence clearly illustrates this. The basic requirements of the architectural principles, namely, "1. The graft should be placed with its long axis in compression rather than in tension; 2. The breadth of the graft should be placed in the position of maximum stress; 3. A joint should be locked by two grafts crossing each other in the shape of the letter X; 4. There should be adequate protection of the graft," form the basis of the laws of bone repair in general, and, this emphasis, alone, would justify the publication. J. M.

OCCUPATIONAL TUMORS AND ALLIED DISEASES. By W. C. HUEPER, M.D., Assistant Director and Principal Pathologist, Warner Institute for Therapeutic Research, New York City. Pp. 896; many illustrations, 3975 references. Springfield, Ill.: Charles C Thomas, 1942. Price, \$8.00.

THE ever-increasing interest in the problem of cancer as well as in the diseases associated with modern industry give this book a twofold value. After an introductory chapter surveying the significance of exogenous factors in the production of carcinoma, the author devotes himself to a consideration of the various organ systems and the causes produced therein by chemical and physical agents. The diversity of these substances is matched only by the enormously varied industries in which they occur. The total number of cases attributed specifically to a certain chemical in a particular industry are frequently quite small and one is reminded of the early bacteriologists who ascribed a particular disease to any and every bacterium they found in the tissues. The author, however, has admittedly attempted to include all available data, and his extensive bibliography will enable the sceptic to refer to the original sources and decide for himself.

The medico-legal aspects of the problem are considered in a separate chapter, as well as in the discussion of the individual lesions. The comprehensive index and good format add to the value of the book. It should be of interest to students of cancer, public health, and general medicine. H. S.

FUNDAMENTALS OF ANESTHESIA, An Outline by the Subcommittee on Anesthesia of the National Research Council. Pp. 217; 72 illustrations. Chicago: American Medical Association Press, 1942. Price, \$2.50.

THIS manual is primarily intended for the instruction of medical officers as anesthetists. It has, however, a much wider field of usefulness particularly in the present emergency, where the administration of depressant drugs and the care of patients with respiratory and circulatory depression will be often in the hands of the inexperienced.

Written by a group of leading United States anesthetists, the outline is up to date in its coverage of inhalation, intravenous, and regional anesthesia. It covers the use of orally administered narcotics, but in a necessarily dog-

matic form. Its chief importance, however, is found in its sections on the management of depressed states of the respiratory and circulatory systems, whether these be due to narcotics, shock, surgery, and so forth.

One can recommend this small volume unhesitatingly to medical students, interns and residents who may soon join the armed forces. It will also prove useful to older physicians who may be called as medical officers with combat troops and who have forgotten the special problems discussed above. For semi-trained anesthetists it will be a valuable guide in the acquisition of skill in the more complicated phases of technical anesthesia since both fundamental techniques and more advanced methods are covered.

R. D.

CABOT AND ADAMS PHYSICAL DIAGNOSIS. By F. DENNETTE ADAMS, M.D., Harvard Medical School, Massachusetts General Hospital. Thirteenth Edition. Pp. 888; 399 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$5.00.

It has been noted recently that doctors entering the armed forces have manifested an outstanding deficiency in their physical diagnostic skill. This may be a reflection of the progressive de-emphasis that this subject has received in our teaching institutions. Perhaps, then, this publication is timely in once again lucidly and systematically presenting the well-established principles of the bedside examination.

That this book is one of the foremost in its field is obvious since it is now in its 13th edition. The 12th edition was a thorough revision and enlargement of the previous text. This edition represents lesser changes. The sections on the mouth, back, pulse, classification of heart murmurs and coronary heart disease have been thoroughly reorganized. The newer ideas on shock are concisely summarized in the chapter on congestive failure by the addition of a section on inadequate cardiac output. The list of clinical entities discussed has been enlarged and minor changes have been introduced where deemed beneficial by the author. The author has drawn freely from the experiences of his colleagues at the Massachusetts General Hospital. These men constitute some of the most eminent physicians in American medicine. Needless to say, the factual material is well grounded.

As a text for beginners one criticism is suggested. Physical diagnosis is frequently introduced to the medical student as his first clinical subject. The discussion of clinical entities, as it occurs in this book, is inaccessible to the young student. Teachers of physical diagnosis recognize the inefficiency and fruitlessness of discussing clinical syndromes with the preclinical student in physical diagnosis classes. However, for the upper class student and the practising physician this book is highly recommended. It is a worthy addition to any doctor's library.

D. T.

GRAY'S ANATOMY. By HENRY GRAY, F.R.S., Late Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Edited by WARREN H. LEWIS, B.S., M.D., Member, The Wistar Institute of Anatomy and Biology, Philadelphia. Twenty-fourth Edition. Pp. 1428; 1258 figures, mostly in colors. Philadelphia: Lea & Febiger, 1942. Price, \$12.00.

THE latest edition of this time-proven classic presents a most thorough revision. In addition, the Editor has obtained the assistance of 6 well-known anatomists as his associates, representing a unique departure from previous editions. Although the arrangement of chapters and subject matter that have characterized the book for so many years remains un-

changed, the text has been revised, rewritten and augmented by the latest information. Many new illustrations are included. Thirty roentgenograms stress the important rôle of roentgenography in anatomy as well as in medicine and surgery. These have been introduced in the chapter on Surface and Topographical Anatomy. The book has grown in size by only 47 pages, but its value to the students has increased tremendously. Thus, this new edition of an old standby can only increase its well-deserved popularity.

D. C.

THE DYNAMIC STATE OF BODY CONSTITUENTS. By RUDOLPH SCHOENHEIMER, Late Associate Professor of Biological Chemistry, Columbia University. Pp. 78. Cambridge: Harvard University Press, 1942. Price, \$1.75.

THIS is a monograph embracing the three Harvard University 1941 Edward K. Dunham Lectures for the promotion of the medical sciences. They were presented by Dr. Hans T. Clarke following the sudden death of the author. It is of primary interest to biochemists and clinicians interested in these problems. These lectures develop "a concept of metabolic 'regeneration,' wherein the central idea is the continual release and uptake of chemical substances by tissues to and from a circulating metabolic 'pool.' Coincident with these cyclic processes there occur among the components of the pool multitudinous chemical reactions, of which only relatively few are concerned with elimination of waste products."

R. B.

A TEXTBOOK OF NEURO-ANATOMY. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Third Edition. Pp. 518; 307 figures. Philadelphia: Lea & Febiger, 1942. Price, \$6.00.

THIS book gives a reliable account of the parts of the nervous system and their interrelationships, rather than detailed descriptions of cellular structure. The chapter on the thalamus now includes a modern consideration of its functional relationships and a section on the hypothalamus. Many of the cuts are reproduced better than in previous editions. The authoritative chapter on the autonomic system still remains one of the best in the book.

W. A.

CORRECTION.—The price of the *International Journal of Sex-Economy and Orgone-Research*, reviewed on page 290 of the August, 1942, issue was given as \$5 a year—the correct price is \$3.

NEW BOOKS

A *Handbook of Allergy for Students and Practitioners*. By WYNDHAM B. BLANTON, M.A., M.D., LITT.D., Professor of Clinical Medicine and Chief of the Immunology Clinic, O.P.D., Medical College of Virginia, Richmond, Va. Pp. 190; 20 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.00.

Medical Progress Annual. Vol. III-1942. Edited by ROBERT N. NYE, M.D., Managing Editor of *The New England Journal of Medicine*. Pp. 678; several figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

A *Short History of Cardiology*. By JAMES B. HERRICK, M.D., Emeritus Professor of Medicine, Rush Medical College; Consulting Physician to Presbyterian Hospital, Chicago. Pp. 240; 48 plates. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.50.

- Professional Adjustments II.* By GENE HARRISON, A.B., R.N., Educational Director, Druid City Hospital School of Nursing, Tuscaloosa, Ala. P. 424. St. Louis: C. V. Mosby Company, 1942. Price, \$3.50.
- Shock, Its Dynamics, Occurrence and Management.* By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Pp. 324; 36 engravings. Philadelphia: Lea & Febiger, 1942. Price, \$4.50.
- CENTRAL AUTONOMIC REGULATIONS IN HEALTH AND DISEASE. With Special Reference to the Hypothalamus. By HEYMEN R. MILLER, M.D., Associate Attending Physician, Montefiore Hospital, New York. Introduction by JOHN F. FULTON, M.D., M.A., D.Phil. (Oxon.), Sterling Professor of Physiology, Yale University. Pp. 430; 61 figures. New York: Grune & Stratton, 1942. Price, \$5.50.
- CASTOR OIL AND QUININE. Once a Doctor, Always a Doctor. By GEORGE W. WATSON VANDEGRIFT, M.D. Pp. 252. New York: E. P. Dutton & Co., Inc., 1942. Price, \$3.00.
- A Bibliography of Aviation Medicine.* By EBBE CURTIS HOFF and JOHN FARQUHAR FULTON. Prepared for the Committee on Aviation Medicine, Division of Medical Sciences, National Research Council Acting for the Committee on Medical Research, Office of Scientific Research and Development, Washington, D. C. Pp. 237. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.00.
- Hospital Discharge Study.* Vol. I: Hospitals and Hospital Patients in New York City. By NEVA R. DEARDORFF, Ph.D., and MARTA FRAENKEL, M.D. Pp. 209; many tables. Welfare Council of New York City, 1942. Price, \$1.00.
- This analysis of 576,623 patients discharged from 113 of New York City's hospitals during the year 1933 is the first attempt at a complete study of morbidity of any large group of patients. The comprehensive data thus developed will be studied by all those interested in morbidity statistics. This work may well be the beginning of a new national morbidity code.
- Outline of Histology.* By MARGARET M. HOSKINS, Ph.D., and GERRIT BEVELANDER, Ph.D., Department of Anatomy, College of Dentistry and the Graduate School of Arts and Science, New York University. Pp. 286; many figures. St. Louis: C. V. Mosby Company, 1942. Price, \$2.50.
- In a striking modern loose-leaf binding, Hoskins and Bevelander have presented a concise outline of histology, profusely illustrated. Part I deals with general histology and Part II, about one third of the book, considers in detail dental histology and embryology. The excellent illustrations are mostly from original pencil sketches. They depict what the student could be expected to see through the microscope. Blank leaves are inserted with each chapter.
- A Manual of Experimental Embryology.* By VICTOR HAMBURGER, Washington University. Pp. 213; many figures. Chicago: The University of Chicago Press, 1942. Price, \$2.50.
- Introduction to Parasitology.* By A. S. PEARSE, Professor of Zoölogy, Duke University. Pp. 357; 448 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.75.
- The Medical Clinics of North America.* Vol. 26, No. 5 (Boston Number). Pp. 306; many figures. Philadelphia and London, W. B. Saunders Company, September, 1942. Price, \$16.00 per year (cloth binding), \$12.00 (paper binding), 6 vol. set.
- X-ray Treatment of Diseases of the Nervous System.* By CORNELIUS G. DYKE, M.D., F.A.C.R., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University; Director, Depart. of Radiology, Neurological Institute of New York, and Leo M. DAVIDOFF, M.D., F.A.C.S., Chief, Depart. of Surgery, Attending Neurological Surgeon, Jewish Hospital of Brooklyn. Pp. 189; 12 engravings, 7 charts, 16 graphs. Philadelphia: Lea & Febiger, 1942. Price, \$3.25.

NEW EDITIONS

An Introduction to Materia Medica and Pharmacology. By HUGH ALISTER McGUIGAN, PH.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois College of Medicine, Chicago, and ELSIE E. KRUG, B.S., R. N., Science Instructor, St. Mary's School of Nursing, Rochester, Minn. Third Edition. Pp. 779; 47 text illustrations, 37 color plates. St. Louis: C. V. Mosby Company, 1942. Price, \$3.50.

First Aid and Bandaging. By ARTHUR D. BELILIOS, M.B., B.S. (LOND.), D.P.H. (ENG.) and others. Fourth reprint. Pp. 628; 239 figures. Baltimore: Williams & Wilkins Company, 1942. Price, \$1.75

War and the Doctor. Essays on the Immediate Treatment of War Wounds. Edited by J. M. MACKINTOSH, M.D., Chief Medical Officer of the Department of Health for Scotland. Second Edition, reprinted. Pp. 135. Baltimore: William Wood & Co., 1942. Price, \$2.00.

A Curriculum for Schools of Medical Technology. By ISRAEL DAVIDSOHN, M.D., Director of Laboratories and Pathologist, Mt. Sinai Hospital, Chicago; Assistant Professor of Pathology, College of Medicine of the University of Illinois. Second Edition. Pp. 47. Muncie, Ind.: Published by Registry of Medical Technologist, Ball Memorial Hospital.

Human Pathology. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. Sixth Edition. Pp. 817; 460 illustrations and 16 color plates. Philadelphia: J. B. Lippincott Company, 1942. Price, \$10.00.

This new edition of Karsner presents a thorough revision of an excellent text. The format has been changed, with 2 columns to the page for easier reading. A section on vitamin deficiencies has been added. The chapter on neoplasia has been almost entirely rewritten to incorporate the results of recent research. The chapter on the principles of infectious diseases has been enlarged. The bibliography has kept pace with the changes in the text and constitutes, as in previous editions, a most valuable feature of the book. These are but a few of the numerous changes and additions that have brought this book up-to-date. About half the text has been entirely rewritten and much of the remaining material has been rearranged. Well over a 100 new illustrations have been provided and photographs and photomicrographs largely replace the older drawings.

The Reviewer finds the book easier to read than previous editions and strongly recommends it, not only as a sound reference, but as an interesting and readable text. It is, in his opinion, the best one-volume textbook of pathology available.
D. C.

Pharmacopœia of the United States of America. Twelfth Revision. By authority of the U. S. Pharmacopœial Convention meeting at Washington, D. C., 1940. Prepared by the Committee of Revision and Published by the Board of Trustees. Pp. 880. Easton, Pa.: Mack Printing Company, 1942. Price, \$7.50.

Comparative Vertebrate Anatomy. By LIBBIE HENRIETTA HYMAN, Research Associate, American Museum of Natural History, New York City. Second Edition. Pp. 544; 136 figures. Chicago: Univ. of Chicago Press, 1942. Price, \$3.50.

This is a revision of the Laboratory Manual for Comparative Vertebrate Anatomy so popular for 20 years. In this edition the textual material has been elaborated so that the book can serve as a text as well as a laboratory manual. Some illustrations are new, and all are taken from the specimen.
W. A.

Fractures and Dislocations. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Surgery (Rush) of the University of Illinois; Attending Surgeon, Presbyterian Hospital; Formerly Attending Surgeon, Cook County Hospital, Chicago, Ill. Fourth Edition. Pp. 1106; 1140 engravings. Philadelphia: Lea & Febiger, 1942. Price, \$12.50.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
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PROGRESSIVE THERAPEUTICS AS AIDED BY U. S. PHARMACOPEIA XII

As was pointed out in the May issue of this Journal, the laborious task of the Twelfth Revision of the United States Pharmacopeia has recently been completed. The object of this revision was to bring into the Pharmacopeia the progress relating to therapeutic agents that had been made in the course of the past few years. There can be little doubt that most physicians regard the Pharmacopeia as an important text, since it provides the legal standards for the quality and purity of medicinal agents. More and more physicians have come to prescribe drugs with the term "U.S.P." written after the name, or to use the official title for a drug which insures that a preparation of Pharmacopeial quality will be dispensed. To the extent to which that is done, the Pharmacopeia comes directly into the practice of efficient therapy. Beyond that, however, physicians make very little use of the Pharmacopeia, since they justly think that the details of matters concerning standards and purity are more directly in the domain of the pharmacist and manufacturer than in that of the practising physician. They seldom turn to the Pharmacopeia for therapeutic assistance, since the text contains no direct therapeutic discussions.

We wish to call particular attention, however, to one aspect of the work of Pharmacopeial revision which makes this text, from one standpoint, one of the most important sources of therapeutic information available to the physician, namely, the aspect of scope. What is new in the field of therapy? Do these new preparations represent essential advances, or are they merely duplications and non-essential modifications of old remedies? How do matters stand with the preparations that have been in use during the past decade? No greater burden rests upon the physician who seeks to practise the most advanced and rational therapeutics than the one of selection of drugs. The literature which

usually brings these matters to his attention is voluminous, confusing, and often represents some specific bias. The course of therapeutic progress is devious and difficult. The Scope and Therapeutics Committees of the Pharmacopeia deal specifically with these problems. The selection of drugs is based upon intensive discussions and deliberations of a group of experts in the various fields to which these agents are applied, including physicians, pharmacologists, chemists and pharmacists, representing sufficiently wide experience to insure the inclusion of diversified views. The "additions" as well as the "deletions" of the new Pharmacopeia represent their decisions.

It is the object of this second section of the review to point out, by brief accounts of a few of the more important groups of therapeutic agents which have been adopted in the Twelfth Revision, the type of considerations which go into the final selection of the list of Pharmacopeial drugs. If the physician will familiarize himself with the agents described in the new Pharmacopeia, he will have gone a long way toward solving a very trying problem, on the one hand, of insuring the fact that he does not overlook many significant developments in therapeutics, and, on the other hand, of escaping the deluge of so-called new preparations which have contributed almost nothing of intrinsic value to the efficacy of therapeutic practice. No text other than the Pharmacopeia sets that up as one of its major functions. It should be noted that the discussions of the few groups of agents which follow are intended merely to be illustrative. To consider all the agents of the Pharmacopeia in this manner would carry this review beyond its proper limits.

Antacids. The previous Pharmacopeia described standards for the following antacids: Sodium Bicarbonate, Magnesium Carbonate, Magnesia Magma (Milk of Magnesia), Magnesium Oxide (light), Heavy Magnesium Oxide, Precipitated Calcium Carbonate, Prepared Chalk and Tribasic Magnesium Phosphate. These are described in the forthcoming Pharmacopeia, in addition to four new types of preparations: Tribasic Calcium Phosphate, Aluminum Hydroxide Gel, Dried Aluminum Hydroxide Gel and Magnesium Trisilicate.

The available aluminum hydroxide preparations of commerce vary in their aluminum oxide content, and in their power to absorb acid. The U.S.P. standards require that the aqueous suspension in the form of the gel represents approximately 4% Al_2O_3 , and that the average dose of 8 cc. (2 teaspoonfuls) consumes between 100 and 200 cc. of 0.1 N hydrochloric acid. The dose of Dried Aluminum Hydroxide Gel is given as 0.6 gm. (10 grains), and this is required to consume at least 150 cc. of 0.1 N hydrochloric acid.

Magnesium Trisilicate is tested for its power to adsorb methylene blue and also for its acid-consuming capacity. The U.S.P. dose of 1 gm. (15 grains) is required to consume approximately 150 cc. of 0.1 N hydrochloric acid. Standards are provided for a Magnesium Trisilicate Tablet. The 0.5 gm. ($7\frac{1}{2}$ grains) size is usually prescribed. In the form of the tablet the acid-consuming power is somewhat less, namely about 100 cc. 0.1 N hydrochloric acid per gram.

With these new compounds in the Pharmacopeia, advanced principles in antacid therapy are recognized, namely, the control of acidity by physical absorption and reduction of acidity of the gastric juice without complete neutralization or alkalization of the gastric contents. These

compounds reduce the hydrogen ion content of the gastric juice but do not possess the power to alkalinize. In addition to removing hydrogen ions, they exert astringent and coating properties. The trisilicate of magnesium especially forms an adherent gelatinous coating with protracted antacid properties of protective and healing value in peptic ulcer.

The Tribasic Calcium Phosphate (dose 1 gm.; 15 grains) serves not only as an antacid but as a useful source of calcium and phosphorus. This is of some importance, in view of the recent evidence that aluminum hydroxide may precipitate the non-absorbable aluminous phosphate and thereby deplete the body of phosphorus stores, leading to phosphorus deficiency.

Sedatives and Hypnotics. The Pharmacopeia now includes four classes of agents in this group: barbiturates, chloral hydrate, bromides and paraldehyde. Among the barbiturates, Barbitol, Barbitol Sodium, Phenobarbital and Phenobarbital Sodium represent the older preparations. Their duration of action is long. The addition of the Elixir of Phenobarbital meets the need for a liquid barbiturate preparation. It contains 15 mg. ($\frac{1}{4}$ grain) of Phenobarbital to the teaspoonful. It is especially useful in children. Pentobarbital Sodium has been added as a representative of the rapidly acting barbiturates. For sustained action as a sedative during the day, Phenobarbital is most useful. It may also be used in the same or somewhat larger doses at bedtime to promote sleep. Barbitol may be used in a similar manner, although it is more commonly employed in the form of a 5 grain tablet at bedtime. With respect to their therapeutic actions, Barbitol and Phenobarbital are interchangeable. There is a significant difference in their mode of elimination. The largest part of a dose of Barbitol is excreted by the kidney, while in the case of Phenobarbital, only a small part of the dose is excreted in this manner, the rest being destroyed in the body. If it is necessary to secure somewhat stronger action to induce sleep, one often finds that Pentobarbital Sodium is more satisfactory, since a larger dose may be given, 0.1 to 0.2 gm. ($1\frac{1}{2}$ to 3 grains), with less risk of a protracted hangover the following day. The sodium salts of the barbiturates are soluble and somewhat more rapidly absorbed than the parent substances. They are particularly important in relation to the use of barbiturates by parenteral administration. The only one that can be given subcutaneously is Phenobarbital Sodium. Its solution is nearly neutral, while the solutions of the other barbiturates are strongly alkaline and irritant. The introduction of standards and methods for the assay of tablets and capsules of the barbiturates gives further assurance of uniformity among the dosage forms in which these compounds are most commonly employed.

In cases of epilepsy, in which very large doses of bromides are sometimes given, there are occasions when large amounts of sodium base are undesirable, and others in which large amounts of potassium might prove harmful. The Pharmacopeia has therefore included both Sodium Bromide and Potassium Bromide. Calcium Bromide and Ammonium Bromide have been deleted as unnecessary duplications. Carbromal, one of the hypnotics of the urea group, has been dropped. It has a very limited sedative action which can be satisfactorily secured from small doses of Phenobarbital.

It is important to have at one's command more than one sedative or hypnotic agent because of the special problems presented by different patients. Often the patient is hypersensitive to one and not to another. On the other hand, the large number of hypnotic agents available in commerce represents a great deal of duplication which leads only to confusion and inefficient therapy. The simplified list of preparations in the new Pharmacopeia meets all essential needs.

Diuretics. The rôle of diuretics in the medicinal control of cardiovascular disorders has increased greatly in recent years. Knowledge concerning the conditions to which these may be usefully applied, their dosage and methods of administration, has made great strides. The Scope and Therapeutics Committees of the Pharmacopeia have selected from the large number of available preparations a small group of the most effective compounds. A diversity of therapeutic indications are taken into account.

Among the xanthines there are Theophylline, dose 0.2 gm. (3 grains); Theophylline Ethylenediamine, dose 0.2 gm. (3 grains); and Theobromine and Sodium Acetate, dose 0.5 gm. ($7\frac{1}{2}$ grains). Standards for the most frequently used dosage forms are described: Theobromine and Sodium Acetate Capsules, Theophylline Tablets, Theophylline and Sodium Acetate Tablets, and Theophylline Ethylenediamine Tablets. While they all possess the same type of diuretic action, there is taken into account the belief that some patients tolerate one of the xanthines better than another. The doses stated are not strictly comparable in terms of the purine base, but are sufficient as a starting point in therapy.

Some patients are so sensitive to the central stimulant action, or to the local irritant action of the entire group of xanthine diuretics that wakefulness, nervousness, or digestive upsets occur before sufficient is taken to affect the edema. In such cases Urea or Ammonium Chloride may be substituted. The Urea is given in such large doses, often as high as 1 ounce 3 times a day, that it is best prescribed in a powder with directions to dissolve the dose in chilled sweetened orange juice. The Pharmacopeia describes standards for Ammonium Chloride Capsules of 1 gm. (15 grains) each, and 1 or 2 capsules are usually taken every 4 hours, although much larger doses are sometimes needed. It is frequently prescribed in enteric coated tablets to overcome the irritant action in the stomach, although there is a good deal of doubt as to whether that result is accomplished by the enteric coating.

The organic mercurials are included for those cases in which oral diuretics do not suffice. The new Pharmacopeia describes these in the form of ampoule solutions: Mercurphylline Injection (Mercupurin) and Mersalyl and Theophylline Injection (Salyrgan with Theophylline). As indicated by the Pharmacopeial directions, experience seems to favor the intramuscular route, and the 1 cc. dose of the former and the 2 cc. dose of the latter, although both doses are used for both preparations, and the intravenous route is frequently preferred. It is noteworthy that, while the previous Pharmacopeia described the mercurial alone, the present one directs the use of the combination with a xanthine. The new text has taken account of the more recent evidence indicating that the addition of a xanthine to an organic mercurial reduces the local irritant action and toxicity. It is important to have more than one

organic mercurial available because there are patients hypersensitive to one who show no intolerance to another.

For the groups of edematous patients, especially those with chronic nephritis, in whom all the foregoing are sometimes ineffectual, Potassium Nitrate or Potassium Chloride are sometimes of great benefit. The potassium salts lead to the accumulation of potassium base and excretion of sodium which in turn results in a diuresis. Standards are provided for the Potassium Chloride Tablets which may be prescribed in doses of 1 or 2 gm. (15 to 30 grains) 3 times a day.

Antiluetic Agents. While there has been a great deal of active research in the field of antiluetic therapy during the past 10 years, it is noteworthy that no extensive revision in the scope of essential agents has become necessary in the new Pharmacopeia. Scores of arsenic and bismuth compounds and their preparations are marketed, but there is indeed a question whether most of them have brought about any significant improvement in the treatment of syphilis. Such preparations as Bismarsen representing combined arsenic and bismuth therapy in one compound for intramuscular use, and Sobisminol Mass for oral treatment of syphilis have excited a great deal of interest, but they cannot be considered as having established superiority for routine therapy. Mapharsen, the hydrochloride of arsenoxide, although a relatively new compound, has received extensive trial and reports of favorable experience are so abundant that little doubt remains concerning the fact that it will come to play an important rôle in the treatment of syphilis. The largest experience in effective antiluetic therapy, however, relates to the limited group of agents official in the forthcoming Pharmacopeia.

Among the arsenicals, the standards for Arsphenamine and Neorarsphenamine are carried over into the new Pharmacopeia. Tryparasamide, dose 2 gm., is described for the special problems of neurosyphilis. While there is no question of the superiority of intravenous arsenical treatment, there are occasions when the intravenous route is not feasible, especially in children. This need has been met by the inclusion of Sulfarsphenamine, dose 0.45 gm. (7 grains), in the new Pharmacopeia. It is recognized to possess greater toxicity for adults than for children, but there are indications of improvement in the method of manufacture which has reduced its toxicity.

For oral treatment, Sodium Iodide and Potassium Iodide are continued.

There are several mercury compounds. Mercuric Salicylate is an insoluble preparation employed in the form of a suspension in oil. The standards for such an oily suspension are now described under Mercuric Salicylate Injection. The drug is usually administered in a dose of 1 cc. of the suspension by intramuscular injection containing approximately 0.1 gm. ($1\frac{1}{2}$ grains) of Mercuric Salicylate and representing approximately 50 mg. of mercury. Mercuric Succinimide is an organic mercurial compound containing slightly less mercury and represents a very soluble mercury preparation. It is relatively non-irritant by comparison with inorganic soluble mercurials such as bichloride of mercury. It is administered intramuscularly in aqueous solutions in doses of 15 mg. ($\frac{1}{4}$ grain). It is usually available in 2.5% solutions, dose 0.6 cc. The difference in the dosage from that of

Mercuric Salicylate should be noted. The average intramuscular dose of the insoluble salicylate represents about 50 mg. of mercury, while that of the soluble succinimide represents only about 7.5 mg. of mercury. A noteworthy change in the new Pharmacopeia is the reduction in the number of mercury compounds for the treatment of syphilis which represented unnecessary duplication. The Yellow Mercurous Iodide has been deleted. Also, in line with the diminishing use of oral antiluetic mercurial therapy, oral doses are no longer provided in the Pharmacopeia for Mercury Bichloride and Mercuric Succinimide. The only mercurial preparation for oral administration of mercury as an antiluetic agent contained in the present Pharmacopeia is the Mercury with Chalk prescribed in an average dose of 0.25 gm. or 4 grains, representing 95 mg. of mercury.

Among the bismuth preparations there are included Bismuth and Potassium Tartrate, and the Bismuth Subsalicylate. The Bismuth and Potassium Tartrate is a compound very soluble in water and rapidly absorbed. It is administered by intramuscular injection in an average dose of 0.1 gm. ($1\frac{1}{2}$ grains), representing about 62 mg. of bismuth. This compound must be stored in light-resistant containers because it darkens on exposure to light. The Pharmacopeia provides standards for the two common dosage forms in which this material is administered, namely, in the form of an aqueous solution in which the absorption is most rapid, and an oil suspension in which the absorption is delayed. The usual aqueous preparations contain 50 mg. of the compound in 2 cc., and the oil suspensions 100 mg. in 2 cc. The oil suspension of Bismuth and Potassium Tartrate is often given in twice the dose of that in the form of the aqueous solution and the intervals between injections are usually 7 days in the case of the oil suspension as against 2 to 3 days in the case of the more rapidly absorbed aqueous solution.

Bismuth Subsalicylate is an insoluble compound. The new Pharmacopeia provides the standards for the Bismuth Subsalicylate Injection, the oily suspension in which it is usually employed. The average dose is 0.1 gm. ($1\frac{1}{2}$ grains) by intramuscular injection, representing about 57 mg. of bismuth, and is commonly available in the oily suspension containing this dose in 1 cc. Bismuth Subsalicylate appears to be the most widely approved bismuth preparation for the treatment of syphilis.

Vitamins. The forward strides in vitamin research in recent years and the avalanche of vitamin preparations of commerce have created a state of confusion bordering on chaos in therapeutics. Some of the earlier discoveries of vitamins were made in relation to a search for the cause of well-known diseases such as pellagra, beriberi and scurvy. When the purified materials were isolated, physicians were in possession of considerable knowledge of the uses to which they could be put. It is otherwise in the case of several of the vitamin compounds more recently brought to light. The search for the latter was correlated more directly with the growth and metabolic abnormalities in experimental animals. For example, pantothenic acid was developed in relation to the cure of the nutritional dermatitis of chicks, pyridoxine in relation to the cure of the pink or florid dermatitis (acrodynia) in rats kept on a deficient diet, vitamin E (wheat germ oil or alpha-tocopherol) in relation to the prevention or cure of neuromuscular degeneration and reproductive

disorders due to dietary deficiencies in lower animals. Little is known, however, of the rôle of these and other of the newer vitamins such as biotin and choline in human disorders, although numerous suggestive observations in man have been made. An authoritative expression on the scope of the therapeutically effective vitamins by the Pharmacopeia is therefore very welcome.

The widely different compositions and potencies of market preparations present another trying problem for the practitioner. There is the further fact that he should be assured not only that the labeled potency is correct, but that the method by which potency is determined gives results which are applicable to humans. There are several methods of assay for most of the vitamins, and they do not always give the same results when two materials are compared. There is evidence, for example, that, in relation to vitamin D, the liver oil of the blue-fin tuna is about 6 times as effective in the rat as in the chick, while the oil of the white sea-bass is only about one-half as effective in the rat as in the chick. This is probably due to the different composition of specific sterols in the two oils, one of which is more effective in one species than in the other. The selection of a proper bioassay method which will establish constant potency of vitamin materials for man is, therefore, a matter of major importance.

The previous Pharmacopeia described only two materials for their vitamin content, vitamins A and D, in the form of Cod Liver Oil (dose 8 cc. daily or at least 600 units of vitamin D and 6000 units of vitamin A), and the Emulsion of Cod Liver Oil (dose twice as large). These doses provide adequate intake of the two vitamins for prophylactic purposes. At this point it may be stated that all the Pharmacopeial doses of vitamins apply to prophylaxis. Larger amounts are usually necessary in established deficiency diseases. The subject of the vitamins was given intensive study by several subcommittees of the U. S. Pharmacopeial Revision Committee, the committees on Scope, Therapeutics, Bioassay, and the U.S.P. Vitamin Advisory Board. The essential progress of the past 10 years has now been incorporated in the new text. There are described suitable preparations of all the vitamins of established value, proper dosage forms, methods of assay, and average dosage.

For the treatment of vitamin A deficiencies (night blindness, xerophthalmia, follicular keratosis), the Pharmacopeia provides a rich source of vitamin A in the preparation, Oleovitamin A. This preparation represents a concentrated solution in oil of natural vitamin A obtained from fish liver sources. It is required to contain at least 50,000 units of vitamin A per gram (above 50 drops) and not more than 1000 units of vitamin D. It is more suitable as a clinical source of vitamin A than Cod Liver Oil. The prophylactic daily dose of this preparation is 0.1 cc. ($1\frac{1}{2}$ minims or 5 drops), representing at least 5000 units of vitamin A with a negligible amount of vitamin D (100 units or less). To obtain the same amount of vitamin A it would be necessary to give 2 teaspoonfuls of Cod Liver Oil which has, from certain standpoints, the further disadvantage of the presence of large amounts of vitamin D. The Pharmacopeia also describes Oleovitamin A capsules, one containing 5000 units and the other 25,000 units. One of these smaller capsules daily is used for prophylaxis, and the latter for massive dosage in

treatment. It is noteworthy that for vitamin A therapy the Pharmacopeia does not provide any carotene preparations or synthetic materials of vitamin A. The use of vitamin A parenterally also seems to be too unsettled for routine application.

As a concentrated source of vitamin D for the prevention and treatment of rickets and other vitamin D deficiencies, the new Pharmacopeia describes the preparation Synthetic Oleovitamin D (viosterol in oil, activated ergosterol in oil). It is provided only in solution because dry pure viosterol loses potency fairly rapidly. The text requires that the label shall indicate whether the preparation contains vitamin D₂ or vitamin D₃, because there is some doubt as to the identity of their actions in man. In this connection it should be noted that there are several antirachitic sterols from vegetable and animal sources. The two most important ones are ergosterol (from vegetable sources) and 7-dehydrocholesterol (from animal sources). These compounds are isomers and acquire antirachitic functions through the action of specific radiant energy (ultraviolet rays) which leads to a shift of the position of the double bond in the molecule. This process is referred to as activation. Activated ergosterol is a crystalline compound also called vitamin D₂, and activated 7-dehydrocholesterol is also called vitamin D₃. These two vitamin D sterols have different relative potencies in different species of animals. In the chick, the rat unit of the vitamin D derived from cholesterol (D₃) is nearly 20 times as effective as the rat unit of vitamin D derived from ergosterol (D₂). The vitamin D from the two sources is therefore not identical, although the evidence indicates that their behavior in man parallels fairly closely their behavior in the rat. The rat method, therefore, has been adopted by the Pharmacopeia for the standardization of vitamin D materials.

The preparation Synthetic Oleovitamin D has the advantage over Cod Liver Oil for the prophylaxis and treatment of rickets that it is highly concentrated, it is odorless, and has a bland taste. It contains not less than 10,000 U.S.P. units of vitamin D per gram. Since the prophylactic requirement is only about 1000 units daily, at least this amount will be present in a dose of the oil of 0.1 cc. or 1½ minims or 5 drops. It has the further advantage over Cod Liver Oil that large doses of vitamin D can be administered without simultaneous use of the large amounts of vitamin A present in Cod Liver Oil.

For the problems of mixed fat-soluble vitamin deficiencies in which it is desirable to use both vitamins A and D, the Pharmacopeia provides 4 new preparations, namely, Cod Liver Oil, Emulsion of Cod Liver Oil, and 2 new preparations, Oleovitamin A and D, and Concentrated Oleovitamin A and D. The Oleovitamin A and D is intended as a substitute for Cod Liver Oil. It is of particular importance in relation to the shortage of natural Cod Liver Oil at the present time. The vitamin A in this preparation comes from natural fish liver sources, and the vitamin D content may be either from synthetic or natural sources. The dosage is the same as for Cod Liver Oil, 8 cc. or 2 teaspoonfuls representing approximately 700 units of vitamin D and 7000 units of vitamin A. The potency of this preparation is likely to be more uniform than that of Cod Liver Oil because, while the Pharmacopeia fixes its potency, the text specifies only a minimum potency for Cod Liver Oil. There remains to be considered, however, the possibility that

there may be factors of therapeutic value in Cod Liver Oil which are not disclosed by the specific tests for vitamins A and D.

The preparation Concentrated Oleovitamin A and D provides a highly concentrated source of both vitamins A and D. It represents for the most part a combination of the preparations Oleovitamin A and Synthetic Oleovitamin D. The standards require a fixed content of both vitamins A and D. The daily prophylactic dose of this preparation is 0.1 cc. ($1\frac{1}{2}$ minims or 5 drops), representing approximately 5000 units of vitamin A and 1000 units of vitamin D. This is an extremely useful preparation for both the prophylaxis and the treatment of conditions requiring the combination of the two vitamins. A dose of 5 drops of this preparation provides approximately the same amount of vitamins A and D as is found in a 2 teaspoonful dose of a good grade of Cod Liver Oil. This dose is contained in the Pharmacopeial Capsule of Oleovitamin A and D. The capsule is a convenient dosage form, 1 capsule daily being required for prophylactic purposes.

For the treatment of alcoholic polyneuritis, the beriberi heart and the wide variety of conditions associated with vitamin B₁ deficiency, the Pharmacopeia provides the preparation Thiamine Hydrochloride with an average daily dose of 5 mg. ($\frac{1}{12}$ grain). The chemical method of assay is described for this compound. There is also included the tablets of Thiamine Hydrochloride which are generally provided in sizes of 3, 5 and 10 mg. The potency of these tablets is assured by a detailed colorimetric test described in the Pharmacopeia. The text also describes a biologic test, the rat method, involving the cure of polyneuritis in rats, for assaying the thiamine content of preparations containing this vitamin. It should be noted that the elixir of thiamine hydrochloride, which is fairly popular, is not included because of the instability of such liquid preparations. The Pharmacopeia also includes Rice Polishings (Tikitiki) as a rich crude source of the antineuritic vitamin.

Nicotinic Acid is the most important single member of the B complex responsible for the curative effects of such food products as liver, wheat germ and yeast in the multiple deficiency disease known as pellagra. The synonym Niacin has been adopted in order to avoid the confusion with nicotine, the toxic alkaloid of tobacco. The average dose of Niacin, as given by the Pharmacopeia, is 25 mg. ($\frac{3}{8}$ grain). Much larger doses are often used. Standards are also provided for Nicotinic Acid Tablets, of which the common sizes are 25, 50 and 100 mg. Nicotinic Acid often produces a histamine-like flush which is sometimes quite disturbing. This effect is much less pronounced in the amide of Nicotinic Acid. The Pharmacopeia has therefore also included Nicotinamide (Niacinamide), and the tablets of this compound in dosages similar to Nicotinic Acid. The amide is about 60 times as soluble in water as the Nicotinic Acid. Both forms are desirable at the present time, because it is not satisfactorily established that the two are in all respects interchangeable in therapy. Chemical standards are provided for these pure compounds, as well as for their tablets. In addition, there is included a biologic method of assay for Nicotinic Acid in mixtures in which it may be contained. This method is based on the effect of Nicotinic Acid on the liberation of acid by the *Lactobacillus arabinosis*.

The therapeutic usefulness of other members of the vitamin B group does not appear to be sufficiently established to have warranted their inclusion in the new Pharmacopeia at the time of the preparation of the original text, namely, Pantothenic Acid, Pyridoxine and Choline. There are no well-established human deficiencies which can be ascribed with certainty to the lack of these materials. Nevertheless, they are found in human tissues and undoubtedly play a rôle there. The special conditions arising during the war which may involve gross dietary defects among armed as well as civilian groups make it desirable to have available a concentrated mixture of the members of the B complex in such proportions as seem appropriate from the limited experience that exists. The Supplement to the Pharmacopeia is therefore to describe the standards for Calcium Pantothenate and Pyridoxine Hydrochloride. There is to be a tablet and a capsule, each containing the mixed vitamins of 250 mg. of Liver Extract fortified with the following: 1 mg. of Thiamine Hydrochloride, $1\frac{1}{2}$ mg. Riboflavin, 10 mg. Nicotinamide, 5 mg. Calcium Pantothenate and 1 mg. Pyridoxine Hydrochloride. There is also to be a preparation of a powder of Liver Extract rich in vitamins for oral administration and a similar material in liquid form for parenteral administration. In addition there is to be a solution of Liver Extract rich in B vitamins for parenteral administration, also fortified by the addition of small amounts of the following: Choline, Nicotinic Acid, Pantothenic Acid, Pyridoxine Hydrochloride and Riboflavin.

For the prophylaxis and treatment of scurvy and other vitamin C deficiencies, the Pharmacopeia includes Ascorbic Acid and the Tablets of Ascorbic Acid which are commonly available in doses of 25, 50 and 100 mg. The average daily dose which extensive experience has established is 50 mg. ($\frac{3}{4}$ grain) by oral administration. Chemical and colorimetric methods are described for the standardization and assay of the crystalline compound as well as the tablets.

Antimalarials. The use of cinchona alkaloids in the treatment of malaria presents a special problem at the present time. Prior to the war, about 90% of the world's cinchona bark came from Java. This bark was obtained chiefly from high quinine-yielding trees and represented the chief source of the world's supply of quinine. The Pharmacopeia has included Quinine, Quinidine and their salts for use chiefly in the treatment of malaria, although relatively small amounts are used also in the treatment of disorders of cardiac rhythm. These sources of Quinine have now been shut off by the war in the Pacific, with the result that attention has again been focused on the use of the other alkaloids of the cinchona tree as antimalarial agents. There are now numerous studies indicating that the mixed alkaloids of cinchona bark, even those mixtures relatively poor in quinine, are nearly, if not quite, as effective as Quinine itself in the control of malaria. These mixtures of the alkaloids of cinchona bark are called Totaquine. In view of the fact that the mixtures of cinchona alkaloids from different sources and different barks show wide differences in composition, the new Pharmacopeia has adopted a set of standards for Totaquine which is for the most part now secured from sources in Central and South America. The sources now available have a rather low content of Quinine, and while the U.S.P. XII preparation was at first required to contain not

less than 10% of anhydrous quinine, the difficulty of maintaining this standard in cinchona bark from present sources has led to the proposal to lower the minimum requirements of quinine in Totaquine to 7%. Totaquine as a substitute for quinine is administered in somewhat larger doses than quinine, namely, 0.6 gm. (10 grains), 3 times daily. It is highly probable that little is lost in the efficiency of the treatment of malaria by the substitution of Totaquine. In addition, it provides an antimalarial agent which is less costly than quinine.

Among the synthetic antimalarial substitutes for quinine, the Pharmacopeia has included Quinacrine Hydrochloride and its tablets. This is a bright yellow powder, soluble in water and possessing a bitter taste. Like quinine, it is effective chiefly against the asexual forms of the Plasmodium. The Pharmacopeial dose is 0.1 gm. ($1\frac{1}{2}$ grains), which may be given in the form of the tablet 3 times daily for a period of about 5 days in the average case of malaria. This material is an acridine dye and causes a somewhat persistent yellow staining of the tissues of the patient. Unlike quinine, its excretion is fairly slow and often as long as a month or two is allowed to elapse before a course is repeated. The toxicity of this compound by oral administration is relatively low and it is not apt to cause cinchonism. While there is little doubt about the value of Quinacrine in the average case of malaria, there is still some question regarding the relative efficacy of the two compounds and the specific circumstances under which Quinacrine is preferable to Quinine. The introduction of Quinacrine into the Pharmacopeia, however, is of special importance at the present time, in view of the serious shortage in the available supply of natural antimalarial agents.

Amebicides. For the treatment of amebiasis, 3 preparations are described, Chiniofon, Emetine Hydrochloride and Carbarsone. While all 3 compounds are effective in the cure of amebiasis, they do not represent duplications, because each possesses a special field of usefulness in the treatment of this disease. Amebiasis is essentially an infection of the large intestine with systemic invasion. The parasites are present in the feces, in the wall of the intestine, and within the tissues of the host such as the liver. Chiniofon, one of the iodohydroxyquinoline compounds, is a pale yellow, bitter powder, fairly soluble in water. It has a fairly high amebicidal activity. The Pharmacopeial dose is 1 gm. (15 grains), which may be given 3 times daily by oral administration. It is available in Pharmacopeial Tablets of Chiniofon, 0.25 gm. (4 grains) each. A similar dose may be given as a retention enema in which 1 gm. is dissolved in 200 cc. of water. These doses are repeated daily, usually for a course of about 10 days, and in some cases oral and rectal administration may be combined. The toxicity of this compound is relatively low, since little of it is absorbed, although occasionally enough is absorbed to produce injury of the liver. It is, however, irritant to the gastro-intestinal tract and occasionally causes diarrhea. In view of the limited absorption, this compound is relied upon chiefly for the eradication of the parasites within the lumen of the intestine. Since in most cases of amebiasis the parasites are also present within the tissues, Chiniofon alone is responsible for a very low proportion of complete cures.

In contrast to Chiniofon, Emetine Hydrochloride is used chiefly

for the eradication of the protozoa present within the tissues of the host. This represents for the most part a parenteral form of treatment of amebiasis. The use of ipecac, from which Emetine is obtained, or Emetine itself by oral administration, is unsatisfactory because even subeffective doses are highly emetic. Emetine Hydrochloride is a slightly yellowish soluble powder which is influenced by light and is therefore preserved in light-resistant containers. It belongs to the group of alkaloids. The Pharmacopeia provides the standards for the ampoule solution under the name of Emetine Hydrochloride Injection. The usually available ampoules contain from 20 mg. ($\frac{1}{3}$ grain) to 60 mg. (1 grain) in 1 cc. The injection is given deep into the muscle because of the irritation produced by subcutaneous injection which results in painful nodules. Emetine Hydrochloride is the safest of the amebicidal agents in the treatment of amebic hepatitis and abscess of the liver, but when used alone it also will eradicate the disease in only a small proportion of cases, about 1 in 6, because it has little effect upon the amebæ present in the lumen of the intestine. It is therefore of little value in carriers. It should be noted at this point that in a fairly large proportion of cases, amebiasis produces no symptoms, and in only a relatively small proportion does it give rise to diarrhea. The toxicity of Emetine Hydrochloride is high, bordering closely on the therapeutic doses, and in a large proportion of cases overlapping the therapeutic doses. Bloody diarrhea, cardiac changes and collapse are the outstanding effects. The use of Emetine is most suited for the treatment of amebiasis in the patient confined to bed. The average Pharmacopeial dose is 60 mg. (1 grain) intramuscularly, which may be repeated daily in a course lasting about 10 days. When given in this way, absorption is in evidence fairly promptly (about 30 minutes), but elimination is quite slow, so that traces may still be found in the urine several weeks after the dose. For this reason it is unwise to repeat a course of treatment for at least 2 weeks. It is usually necessary to supplement this treatment with one of the compounds which is more effective upon the organisms present in the lumen of the intestine, such as Chiniofon or Carbarsone.

Carbarsone is a new addition to the Pharmacopeia. It is a pentavalent organic arsenical containing about 28% of arsenic. It is a white powder, almost tasteless, and insoluble in water. It provides a means for the oral treatment of amebiasis and attacks the organisms in all their locations, in the lumen of the intestine as well as in the tissues. It is therefore useful in carriers. It is absorbed through the gastro-intestinal tract and slowly excreted. A course of treatment with this compound is also limited to about 10 days, with intervals of about 2 weeks between courses. The Pharmacopeial dose is 0.2 gm. (3 grains), which may be taken in capsules 3 times daily. The free forms of the protozoa present in the lumen of the intestine are often more effectively eradicated by the rectal administration of the carbarsone in the form of an enema, 2 gm. (30 grains) dissolved in 200 cc. of 2% sodium bicarbonate (the compound is soluble in alkalis) given every other day. This is essentially an ambulant form of treatment. The dangers from Carbarsone are the dangers of other arsenicals, namely, exfoliative dermatitis and hepatitis. As already stated, in cases of

liver disease from whatever cause, Emetine is preferable for the control of amebiasis.

There are still other agents about which useful comment could be made for the aid of the practitioner. These include, for example, some of the approved sex hormones, synthetic vitamin K or menadione, etc. However, space is lacking for detailed comment on these substances. It is hoped that this review, together with the one published in May, may serve to rouse the practitioner's interest in becoming better acquainted with the great value to him which lies between the covers of U.S.P. XII.

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RADIOLOGY

UNDER THE CHARGE OF
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THE PANCREAS—THE SMALL INTESTINE

The Pancreas. The Roentgen study of disease of the pancreas is difficult because the organ cannot be visualized directly and because it is one of the few structures contained within the abdomen which has not yet been made demonstrable through the retention of some radiopaque substance. Because of this, Rendich, Poppel and Cove⁸ stated that it was necessary to resort to indirect methods. These indirect methods had their chief value in the detection of alterations in the contour of contiguous structures, notably the barium-filled duodenum or the distended stomach, resulting from pathologic changes which modified the volume or the form of the pancreas.

They credited Dickson³ with calling attention, in 1923, to pressure deformities of the barium-filled stomach and duodenum produced by carcinoma of the pancreas. Butler and Ritvo,² they stated, reported in 1931 that they had found displacement with widening of the duodenal curve to be significant of pressure from a tumor of the head of the pancreas. Rigler⁹ was quoted as having confirmed the opinion of Butler and Ritvo² in 1933 and to have added the note that in his experience the stomach was often displaced upward and forward in the presence of carcinoma of the body and the tail of the pancreas, while the transverse colon was displaced downward.

Engel and Lysholm,⁴ they found, had described a method for roentgenologic observation of the pancreas in 1934. The stomach was inflated with carbon dioxide and, following this inflation, roentgenograms were made with the patient in the lateral, prone and antero-posterior positions. Enlargement of the pancreas was indicated by an increase in the space which it normally occupied and was made evident by protrusion into the gas-filled stomach from behind. These authors were interested in the findings of Hunt, Hicken and Best⁶ in exploration

of the biliary ducts with the aid of cholangiography during and after operation, published in 1937. The contrast substance was injected, usually through a tube. In the presence of carcinoma of the head of the pancreas, there was no filling of the lower segment of the common duct. The duct was cut off abruptly in the cholangiogram and often in a transverse direction rather than in a tapering or funnel-shaped pattern. The patent proximal portion of the common duct and the cystic duct were unusually widened. A reflux of radiopaque material into the pancreatic duct was observed in 5 of their cases, the duct being filled for a distance of 2 to 9 cm. Such reflux, they considered, depended on the anatomic relation of the common duct, the pancreatic duct, the ampulla of Vater, and the duodenum. It also depended on the terminal sphincteric mechanism. Giordano and Mann⁵ were quoted as having found that reflux was impossible in about one-third of all subjects because the pancreatic and common ducts opened separately into the duodenum.

Rendich, Poppel and Cove⁸ called attention to the dependence of roentgenologic criteria on gross pressure changes. While these gross pressure changes might result from any enlargement of the head of the pancreas, from regional retroperitoneal lymph node enlargement or from the occurrence of any retroperitoneal mass in the pancreatic area, they were of the opinion that experience in the correlation of roentgenologic evidence with characteristic clinical and laboratory findings in a series of cases warranted them in often parenthetically suggesting the more likely specific etiology. Briefly outlining the anatomic relations of the pancreas to contiguous viscera and organs, they stated the signs which, in their opinion, indicated the presence of a mass in the region of the pancreas. Enlargement of the duodenal loop or widening of semicircular arc described by the duodenum might vary according to the habitus of the individual. It could be only an apparent enlargement in the presence of the hypersthenic habitus, in which the stomach is highly placed and almost horizontal in position; the duodenal loop in such individuals when fully exposed appears to be enlarged. Enlargement alone is consequently less significant in the hypersthenic person but very significant in the sthenic or hyposthenic subject. They considered it mandatory in the examination of the hypersthenic type of individuals, who as a group seemed to them to be much more frequently the subjects of biliary tract or pancreatic pathology, to demonstrate, in addition to the enlargement, some evidence of extrinsic pressure on the inner concave border of the descending duodenum. Extrinsic pressure, in their experience, by its ironing-out effect, changed the direction of the medial ends of the horizontal duodenal mucosal folds (*valvulae conniventes*) so that they became internally concentric with the duodenal lumen and were visualized in the roentgenogram as a border limiting the medial wall of the barium-filled descending duodenum. The density of the mucosal folds was directly proportional to the degree of extrinsic pressure from the space-occupying mass in the region of the head of the pancreas. They found this sign to be an early one, discernible prior to the occurrence of any enlargement or displacement. In the presence of severe pressure, the pattern of the *valvulae conniventes* might be greatly altered or even completely obliterated.

Displacement of the duodenal loop toward the right and anteriorly

by space-occupying masses in the region of the head of the pancreas they found to be one of the later signs. The displacement, in their experience, might be general and uniform or it might be simply a localized indentation on the inner concave border of the duodenal loop. They found the stomach to be displaced upward and forward in the presence of a large mass. Enlargements in the region of the body and tail of the pancreas did not affect the duodenal loop but produced downward and anterior displacement of the transverse colon and proximal jejunum and occasional upward and forward displacement of the stomach.

Fixation of the duodenal loop was noted by them, especially of the medial wall. This, they thought, might impair the normal expansion which was usually observed at the time of the passage of increased amounts of opaque medium. Diminished caliber of the lumen of the duodenum was a feature in some cases, sometimes severe enough to result in duodenal obstruction. Alterations in peristalsis were found to be significant; these might be seen as diminishing or even absence of the peristaltic waves. Antiperistalsis might even occur in some cases.

Other characteristic findings were the presence of a palpable mass, the downward and forward displacement of the mid-transverse colon and a filling defect on the outer wall of the descending duodenum with displacement of the duodenum medially. This latter finding, due to an enlargement of the gall bladder, in the presence of painless jaundice of increasing severity, they considered suggestive at least of carcinoma of the common duct or of the ampulla of Vater.

The most common morbid processes occurring in the region of the head of the pancreas that were capable of producing identical roentgenologic signs were, in their experience, malignant new growths involving the head of the pancreas, enlargement of retroperitoneal lymph nodes from (a) primary malignancies, (b) metastatic malignancies or (c) inflammatory lesions, such as infectious mononucleosis, pancreatitis, retroperitoneal tumors, cysts of the head of the pancreas, aneurysm of the anterior wall of the abdominal aorta, amyloidosis of the pancreas and upward traction of the duodenum in some cases of diaphragmatic herniation of the stomach. Pancreatitis might vary from simple edema secondary to involvement of the biliary tract by pathologic processes to chronic pancreatitis with or without biliary calculi.

The pancreas might be the seat of diffuse parenchymal calcification, calculi of varying size and shape might be found in the duct system or a combination of both might be found. The relative frequency of occurrence of each of the individual types was indicated by the fact that Beling, Baker and Marquis¹ were only able to find previous reports of 13 cases of disseminated calcification in their review of the literature on this subject. Calculi, they found, occurred more frequently in the head, less frequently in the body, and comparatively rarely in the tail of the pancreas. Symptoms, all indicative of more or less obstruction in the main ducts, varied widely and might even not present in the earlier stages of the disease. The average age of patients in whom pancreatic calcification occurred was 40 years, but because cases had been reported in which the onset occurred as early as 6 years of age, roentgenograms made of the abdomen of children should be carefully inspected in all doubtful cases. The condition, in their experience,

occurred predominantly in males. Calcification probably occurred secondary to repeated attacks of pancreatitis. Symptoms were usually referable to the gastro-intestinal tract and were severe enough to suggest Roentgen investigation. In a study of the roentgenograms made in 754 consecutive examinations of the gastro-intestinal tract, they found but 1 case showing disseminated calcification and 7 others that suggested calculi in the pancreatic duct system. In the majority of the roentgenograms made in such examinations, the shadow of the opaque media in the stomach or in the colon might obscure the pancreatic area, or flakes of barium in the small intestines might make recognition and differentiation of pancreatic calculi difficult if not impossible. They found it expedient to have a plain roentgenogram made prior to the administration of any type of opaque medium; this should encompass not only the critical area but also the corresponding area to the left of the spinal column. When suggestive shadows were found to be present, further roentgenograms made with the patient in the lateral position were ordered. The indirect methods heretofore described were found helpful. Roentgenograms made in stereoscopic sets were helpful only in those cases where calcifications were found present and they were not considered essential unless other tests were inconclusive. These other tests included blood amylase and lipase determinations and analysis of the pancreatic secretions recovered through an indwelling duodenal tube, both with and without the use of secretin.

The Small Intestine. The incidence of lesions of all types, blastomatous and non-blastomatous, is very low in the small intestine, and the roentgenologic examination of the small intestine, compared to that of the divisions of the alimentary tract above and below it, is an arduous and time-consuming procedure. To many examiners it seemed possible to learn comparatively little about the roentgenologic manifestations of the lesions affecting the lower part of the duodenum, the jejunum and the ileum. Weber and Kirklin¹¹ noted a renewed interest in the application of roentgenologic methods to the diagnosis of lesions of the small intestine in the last decade.

There were certain clinical syndromes in the presence of which the diagnosis of "gastro-intestinal lesion" was imperative, even when all preoperative objective diagnostic tests failed to exhibit the pathologic process responsible for them. Proved gastro-intestinal bleeding was an outstanding example of such an imperative clinical situation. After the esophagus, stomach, duodenum and colon were eliminated as possible sites of the hemorrhagic lesion by the judicious use of roentgenologic and endoscopic tests, it was certainly justifiable to conclude that if a gastro-intestinal lesion existed at all, the small intestine was harboring it. Under most circumstances sufficient grounds for the institution of diagnostic laparotomy might thus be established.

It was better, of course, first to exhaust all other means of localizing the lesion, but these authors felt that a special roentgenologic examination of the small intestine could be made to yield very satisfactory diagnostic results frequently enough, at least, to warrant its application whenever the condition of the patient permitted it.

In a tabulation of 108 cases of malignant lesions of the small intestine, C. W. Mayo⁷ showed the jejunum to be the segment of the small intestine most frequently affected by malignant tumors, while the other

segments, the duodenum and ileum, were involved one about as frequently as the other. In an analysis of the benign lesions of the small intestine seen in the Mayo Clinic from 1907 to 1939, inclusive, Weber and Kirklin¹¹ found the duodenum to be the favored site for the benign lesion. Adenocarcinoma was by far the most frequently encountered histopathologic type of malignant tumor of the small intestine in Mayo's series, while most of the rest of the cases were leiomyosarcoma. A greater variety of histopathologic types of benign tumor were seen, but no one type played so dominant a rôle as adenocarcinoma did among the malignant tumors. The high incidence of tumors of the smooth muscle, both benign and malignant, was noteworthy. The distribution of the various histopathologic types of malignant and benign lesions in the several divisions of the small intestine was shown in 2 tables.

A critical study of the cases in the Mayo series⁷ revealed that there were 36 cases of the 108 in which the diagnosis should have been made roentgenologically. In 4 of the 36 lesions taken for consideration, the lesion was overlooked completely. In the remaining 32 cases (89%), the presence and site, at least, of a pathologic process was determined roentgenologically. Among these 32 cases there were 8 in which more or less serious misinterpretations detracted from the value of the roentgenologic diagnosis. All of these occurred in cases of carcinoma of the first portion of the duodenum.

An analysis of the cases of tumor of the small intestine encountered at the Mayo Clinic during the years 1930 to 1939, inclusive, revealed 62 cases, 50 of which were of malignant tumor, and 12 of benign tumor. Twenty-six were not pertinent from the viewpoint of roentgenologic diagnosis; in 5 of them no roentgenologic examination of any part of the gastro-intestinal tract was made; in 17 no roentgenologic examination of the small intestine was made, although roentgenologic examination of the stomach or colon or of both was made; in 4 a clinically important lesion was diagnosed correctly in the stomach, colon or duodenum. In 5 of the remaining 36 cases (14%), the lesion of the small intestine was overlooked at the roentgenologic examination. Three of these lesions proved on pathologic examination to be adenocarcinoma; 1, lipoma; 1, submucous hemangioma, 6 mm. in diameter, discovered at pathologic examination of a resected specimen of ileocecal granuloma with persistent postoperative fecal fistula. In the remaining 31 of 36 cases (86%), Weber and Kirklin¹¹ considered the roentgenologic diagnoses as satisfactory. While a precise pathologic diagnosis was not made in each instance, the lesion was at least recognized and located where the tumor was later found at operation.

Of 62 cases of tumors of the small intestine, 7 occurred in the first portion of the duodenum, 3 in the second portion of the duodenum, and 7 in the third portion of the duodenum. The lesion was identified in 94% and agreed with the diagnosis on microscopic examination in 53% of cases. There were 20 cases in which the tumor occurred in the jejunum. In 1 case no roentgenologic examination of any part of the gastro-intestinal tract was made; in 6, roentgenologic examination of only the stomach or colon or both was made. Of the remaining 13 cases, the lesion was missed in 2 and in 11 a satisfactory roentgenologic diagnosis was offered. In their experience, the ileum seemed to be the most difficult region of the small intestine from the standpoint

of roentgenologic diagnosis. There were 21 cases in which the tumor proved to be in this segment of the small intestine. Four were benign and 17 were malignant tumors. Fifteen of these 21 cases were not considered to be pertinent to their analysis because in 3 of them no roentgenologic examination of any part of the gastro-intestinal tract was made; in 8, roentgenologic examination of only the stomach or colon or both was carried out; and in 4, a clinically important lesion was correctly diagnosed roentgenologically in a part of the gastro-intestinal tract other than the small intestine. The lesion was overlooked in 2 of the remaining 6 cases; in 4 (67 %), the lesion was recognized at the roentgenologic examination. The ileum, especially in that part of it adoral to its lowermost 12 inches (30 cm.) they found, offered the greatest difficulty in diagnosis, chiefly because it was difficult to maintain a distended concentration of the contrast suspension there, and because these segments tended to seek such a low level in the pelvis that they were elevated from there often with greatest difficulty.

Considering the roentgenologic manifestations of tumors of the small intestine, Weber and Kirklin¹¹ stated that the technique of roentgenologic examination cannot be standardized precisely, because occasionally it must be changed in certain respects to suit individual cases. Briefly stated, the upper segments of the small intestine, the duodenum, the jejunum, and the upper two-thirds or so of the ileum were observed roentgenologically by following the progress of a simple mixture of equal parts of barium sulfate and water through these segments. In their experience, the lowermost third of the ileum was usually studied to best advantage by filling it with contrast suspension in retrograde direction through the ileocecal orifice, roentgenoscopic and roentgenographic examinations being made after the bulk of the contrast material had been expelled from the colon. They were of the opinion that the roentgenoscopic examination was the cardinal roentgenologic maneuver, whether the contrast material was administered orally or rectally, and that no number of interval roentgenograms made without reference to a competent roentgenoscopic examination could supplant it satisfactorily.

Like the colon, they stated, the small intestine was a tubular organ. These divisions of the alimentary tract resembled each other in every important morphologic and physiologic respect. The pathologic processes which occurred in them were similar, and both divisions were deformed by such processes in similar ways. Hence, they were convinced, it was possible to apply the same roentgenologic criteria of diagnosis to the small intestine as had been found reliable in the diagnosis of the normal and abnormal large intestine.

Pathologic processes deformed the tubular segment and it was chiefly by the roentgenologic demonstration of such deformities that the presence of disease was determined. One type of pathologic process was distinguished from others by analysis of the morphologic features of the deformity produced and by interpretation of them in terms of pathologic anatomy. The term "deformity" included the concept of that familiar term in roentgenologic literature, the "filling defect," which may be defined as a subtraction from the normal luminal outline, and the concept antithetic to this, namely, an addition to the normal luminal outline, of which the diverticulum and the penetrating ulcer were

most familiar examples. Tumors, both benign and malignant, deformed all segments of the alimentary tract, especially the simple tubular ones, like the esophagus, small intestine and colon, in a way peculiar to themselves. The deformity produced by a tumor might be marginal or encircling, in whole or in part, such as the one produced by an annular carcinoma, or it might be internal or central, such as is produced by the lesions known as polyps or polypoid lesions. In any case, the "filling defect" produced by tumors not complicated by perforation was relatively short and was sharply demarcated aborally and adorally, and the mucosal pattern throughout the extent of the defect was obliterated.

Tumors, in their experience, arising in the submucous structures frequently did not actually invade and destroy the mucous membrane over them, but when they became large enough to be recognized roentgenologically, they obliterated the mucosal pattern over them if in no other way than by stretching the mucous membrane to the point of obliterating its folds, the basis for the mucosal pattern. They found that tumors of the colon and small intestine often produced obstruction of such a degree that the morphologic features of the lesion were not manifested roentgenologically. In such instances it might be impossible to render a more specific roentgenologic diagnosis than that of obstructing lesion. A similar situation developed in cases of intussusception whether it was entero-enteral, enterocolic or colocolic. In adults primary intussusception was so rarely encountered that for practical purposes it could be said that the condition was not seen except with tumor as its cause.

Attention was called to the fact that tumors and other lesions of organs contiguous to or very near the small intestine might extend to it and involve it segmentally, producing a roentgenologic picture similar in many respects to that produced by primary intestinal tumors. Lesions, especially cysts and tumors, of the pancreas were particularly prone to do this. The roentgenologic evidence of the essentially extra-enteral nature of this process was usually demonstrable at the roentgenoscopic examination. Such extrinsic lesions were usually large and thus careful palpation under roentgenoscopic control would almost always yield the key to the correct diagnosis.

These were the cardinal signs from which the roentgenologic examiner derived the concept of tumor, using that term in its narrower sense to signify blastoma, as distinguished from inflammatory tumors or granulomatous processes. These signs, they stressed, must be understood to be but gross morphologic evidences. It was impossible, as a rule, to derive from them reliable concepts regarding the histopathologic nature of the tumor, such as its malignancy or non-malignancy, and the histologic type of tissue of which it was composed.

Their expressed opinion was that the rule may be stated that there are no reliable roentgenologic evidences of benignancy once the evidence for tumor was produced. Certain lesions might manifest all the so-called classical gross morphologic evidences of benign tumors. Such lesions might, on microscopic examination, prove to be true malignant lesions. They felt that this held particularly true for such tumors when they were found in the gastro-intestinal tract. The roentgenologic examiner, then, since he was dealing with gross morphologic characters of lesions, rarely if ever could elicit diagnostic data on which

he could guarantee the benignancy of a tumor he had discovered. He might say that the lesion he had found "looked" like a benign lesion to him. His opinion might later be proved correct in most instances, but his medical and surgical consultants had best not consider his diagnostic guess too seriously, but prefer to consider the morphologic features he described and treat the lesion as a malignant one until competent histologic study proved its true nature.

Lesions that were not tumors deformed the tubular segments of the intestinal tract in a different way. As a group, they tended to extend over longer segments, producing longer deformities. Demarcation between involved and uninvolved segments, in their experience, was gradual, not abrupt. Depending on the pathologic nature and the severity of the disease producing the deformity, the mucous membrane might or might not be destroyed, and the mucosal pattern was correspondingly altered. Even when the mucosal pattern was obliterated completely by ulceration, however, the mucosal relief had a different roentgenologic appearance than that of the relief pattern of tumors. The experienced roentgenologic examiner, they asserted, recognizes a typical mucosal relief pattern associated with tumors, and especially with malignant tumors. He makes use of his familiarity with this pattern in instances in which a malignant tumor has perforated. In this event the lesion takes many of the morphologic characteristics of the inflammatory, tumefactive processes, and it is only by eliciting what may be called the typical mucosal relief pattern of malignant tumor that the roentgenologic examiner can arrive at a diagnosis of the true nature of such lesions.

These authors felt that roentgenologic examination had a very real contribution to make to the diagnosis of lesions of the small intestine. They acknowledged that roentgenologic examination of this division of the alimentary tract had not approached the efficiency of the roentgenologic method applied to the divisions above and below it. Such efficiency, they thought, perhaps was too much to hope for. They were of the opinion that with accumulating experience improvement would come and, with greater interest in this examination on the part of their clinical and surgical consultants and greater reliance on it, that more lesions would be discovered. It was their hope that accumulating clinical experience would eventually lead to a better selection of cases for roentgenologic examination and that through this many a patient would gain the advantage of earlier treatment than at present for these otherwise, for the most part, hopeless conditions.

That carcinoma of the duodenum was a rare condition and therefore of unusual interest to the clinician and the roentgenologist, was the conclusion of Ritvo and Hewes¹⁰ after the study of the records of all patients admitted to the Pondville Hospital. This institution, under the auspices of the Massachusetts Department of Public Health, is limited to the diagnosis and treatment of growths of a malignant nature and has been functioning for 12 years. Among 16,000 patients admitted and on whom 1655 autopsies were made, only 3 proved cases of carcinoma of the duodenum were found. This incidence rate of 0.02% was in agreement with those reported from the study of other series; these varied from 0.03 to 0.06%.

They found carcinoma of the duodenum to be essentially a disease

of the later decades of life. In their series, the youngest patient was 63 years of age and the oldest 80 years, the average being 70 years. In the cases which they found in reviewing the literature, the ages varied from 37 to 80 years (general average, 48.3 years). This was in striking contrast to carcinoma of the stomach and colon, in which the lesions occurred in patients as young as 13 years of age. Males were affected in the ratio of about 2 to 1.

No constant predisposing factor for carcinoma of the duodenum was determined. There was no apparent relation to peptic ulcer or any other lesion in the gastro-intestinal tract. Nor were there any demonstrable nutritional, occupational, or hereditary factors. None of the patients in their series presented long-standing stomach or bowel complaints. Symptoms were usually of a few months' duration; on only 1 instance did the history extend over a period as long as 2 years.

Their study revealed that carcinoma may occur in any portion of the duodenum. The second portion was frequently involved (62%) and the first portion was the next most frequently involved (25%). Neoplasms were found in the third portion in 13% of cases. Adenocarcinoma arising from the mucosa constituted 90% of the cases. Scirrhus or colloid growths were the rule. Sarcomatous lesions were found in only 2 to 5% of instances. The gross findings were most frequently those of an annular, constricting neoplasm which in some instances completely encircled the lumen. This type was particularly prone to occur in the first and second portions. In the third portion of the duodenum, the growth was more apt to be large and fungating. The sarcomas were usually softer and non-constricting. Stenosis, they found, occurred relatively early and frequently in the lesions involving the duodenal cap. In the neoplasms occurring in the third portion, obstruction was a late and common development. Involvement of the ampulla of Vater was not common. Practically all of the lesions involving the second portion of the duodenum, however, eventually caused obstruction of the bile ducts with resultant jaundice. It was at times impossible to state with certainty whether the growth originated in the duodenum or in the ampulla itself. One case was reported as having occurred primarily in a diverticulum. This was explained by the fact that the mucosa lining the diverticulum was usually the same as that in the duodenum itself.

The clinical symptomatology of carcinoma of the duodenum they found to be indefinite, variable, and usually not pathognomonic. As a rule, the onset was gradual and insidious. Pain might only be slight or it might be absent. When present, it was located in the epigastrium or right upper quadrant, and was usually dull in character, although rarely it might be sharp and colicky. Weight loss was marked and rapid. Vomiting was a feature when the lesion caused stenosis and blood and bile, along with undigested food particles, were frequently present. Anemia was usually severe. Jaundice occurred in about 20% of cases and rarely might be intermittent in character. Biliary colic might be present in the later stages of the disease.

The symptoms were, as a rule, of short duration, the length of time during which complaints were present averaged about 4 months. If the duodenum became completely blocked, the usual manifestations of

obstruction were predominant. Involvement of the ampulla of Vater produced the typical changes associated with jaundice.

In their experience, the physical findings were usually negative in the early stages. As growth progressed, the anemia and wasting characteristic of advancing carcinoma became more evident. A mass in the mid-epigastric region was palpable in about 50% of cases. Frequently there was enlargement of the liver and the gall bladder was palpably enlarged.

Laboratory findings were variable in their cases and often were of little or no aid in arriving at the diagnosis. Increased hydrochloric acid in the gastric contents was present, as a rule. Blood and bile were frequently found in the vomitus and the finding of blood with absence of bile on duodenal drainage was of special significance and indicated to them the possibility of a neoplasm involving the duodenum. Changed blood in the stools or tarry stools occurred, but this finding was not particularly helpful because it was common to so many conditions.

The roentgenologic findings in their cases were in agreement with those already presented.

The differential diagnosis of carcinoma of the duodenum, they asserted, presented especial difficulties because strikingly similar features characterized many other conditions. Carcinoma of the bile ducts or ampulla of Vater with invasion of the duodenum, for example, might be impossible to distinguish from duodenal carcinoma. Carcinoma of the head and body of the pancreas presented roentgenologic characters by which it could be differentiated and obstruction did not result, as a rule, from lesions involving the pancreas.

Lymphoblastoma and lymphosarcoma exhibited definite patterns in roentgenologic examination with simultaneous lesions of the lymphoid structures in various parts of the body and enlargement of the spleen. The rate of growth, as demonstrated by periodic reexamination, was much more rapid than it was in carcinoma. The response to adequate Roentgen therapy was prompt and striking in the lymphoid type of lesions, and this was often of great value in the making of the diagnosis.

Carcinoma involving the stomach, particularly in the region of the pylorus, could usually be differentiated by roentgenologic examination and was also characterized by the absence of free hydrochloric acid in the stomach.

In acute or chronic pancreatitis, there was no change in the acidity of the gastric contents, blood in the vomitus or stools was absent, and the pain which was the outstanding feature of pancreatitis was acute and severe.

Impaction of a gall stone in the duodenum, while of rare occurrence, might be difficult to differentiate from carcinoma of the duodenum. If the stone did not cause complete obstruction, the smooth, round borders would suggest a polyp rather than a malignant neoplasm. With complete blocking of the lumen of the intestine by a calculus, the sharp, rounded superior margins of the stone felt on palpation should suggest the proper diagnosis. Roentgenographic examination of the abdomen prior to administration of a contrast medium might reveal the calculus under favorable circumstances.

Adhesions about the duodenum, either postoperative or as a sequel to pericholecystitis, diverticulum of the duodenum, and deformity

following extensive scarring from the healing of duodenal ulcers might in their symptomatology closely simulate carcinoma of the duodenum. Roentgenologic examination and reëxamination were most helpful in the making of the differential diagnosis and some clinical features were stated that had been found of value.

Duodenal obstruction, they pointed out, might also result from external pressure. Among the chief causes of this they listed: enlargement of the gall bladder, tumors of the omentum, pancreas or liver; enlarged retroperitoneal nodes and other tumefactions in this region; aneurysms of the celiac axis at the hepatic artery; and pressure from the superior mesenteric vessels. If the stenosis was partial or intermittent, differentiation might be possible. With complete obstruction, however, the cause of the stenosis could only rarely be determined.

In the treatment of carcinoma of the duodenum, Ritvo and Hewes¹⁰ found medical therapeutic measures of value as a supportive measure. In the presence of dehydration the administration of fluids orally or by injection methods was indicated. Anemia and lack of adequate vitamin content had to be prevented when possible and sufficiently treated when they presented. Transfusions were administered when necessary. Explorative laparotomy was indicated if the roentgenologic evidence pointed strongly to duodenal neoplasm, as the only hope of relief rested on prompt operative intervention. Surgical relief might be impossible even in the first stages of the disease because of the location of the primary growth, but if intervention was delayed until the diagnosis was established with certainty, it would doubtless be too late to effect a cure. Palliative surgery, such as resection or short-circuiting for the relief of obstruction, should be resorted to whenever necessary as it might serve to diminish suffering and possibly to save life.

Roentgen and radium therapy, in their experience, offered little of real value because of the location of the growth. These measures did, however, offer something as palliative procedures and in the differential diagnosis of lymphosarcomas which, as before mentioned, responded promptly and remarkably to radiotherapy.

The prognosis in carcinoma of the duodenum, they averred, was poor. The average duration of life was 6 to 8 months. The longest period of survival, in their knowledge, was about 2 years. Surgical intervention, while of importance for palliation, did not in the cases reported appear to have any great value in the prolongation of the life of any of these patients.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal of the American Medical Association* with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, *i. e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the more exact meaning.

THE EDITOR.

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1942

ORIGINAL ARTICLES

NON-SPECIFICITY OF GLOMERULAR LESIONS OF THE KIDNEY

BY HENRY A. CHRISTIAN, M.D.*

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THIRTY years ago, busied in a study of experimental nephritis in association with Drs. James P. O'Hare, Richard M. Smith and Chandler Walker, I noted that, whereas the most frequent and most marked renal lesion caused by uranium nitrate in the rabbit was a degenerative one of the epithelium that lined the proximal convoluted tubules, there also occurred lesions in the glomeruli. These lesions in the glomeruli were various; they were discussed in several papers published about that time.^{1,2,3}

Recently, in a study of the renal lesions of subacute *Streptococcus viridans* endocarditis, I have described a variety of lesions in the glomeruli.⁴ Many of these are identical with many of those observed by me and my associates 30 years ago in uranium nitrate nephritis in the rabbit and with those described subsequently by others.

In uranium nitrate poisoning and in subacute *Streptococcus viridans* endocarditis we have effective on the glomeruli a fairly simple inorganic chemical in the former and in the latter a product, probably a complex organic substance, derived from the growth in the human body of a living bacterium. Each can be regarded as an injurious agent acting directly or indirectly on a complex, living structure, *e. g.*, in these examples, the glomerulus of the kidney. They probably are typical of the causative factors of glomerular lesions in many diseased conditions in the kidney.

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If we define inflammation broadly as the reaction of living tissue to the presence of an injurious agent, a definition of inflammation not infrequently given by pathologists, then the majority of the lesions, which have been observed in the glomerulus of the kidney, can be considered to be inflammatory lesions developing in a structure of much complexity. Following injury there are degenerative changes. In turn these initiate proliferative changes. In sequence to proliferation further degenerative changes often occur. Finally reparative processes may appear.

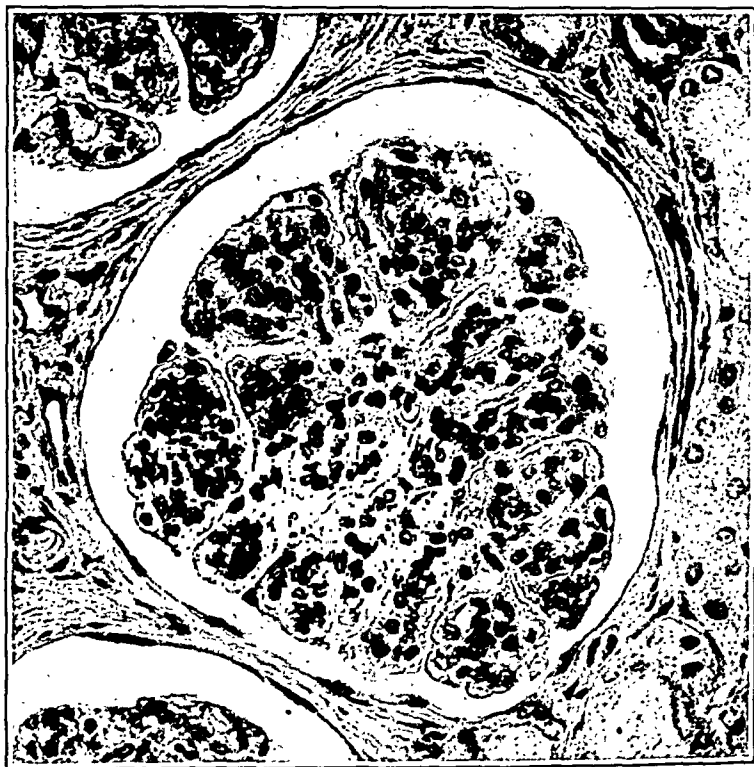


FIG. 1.—Glomerulus from a case of glomerulonephritis, P.B.B.H., Path. No. A 27.8, showing proliferation of cells, mainly intracapillary endothelial cells.

Early in such a process in the glomerulus, evidences of injury may be seen. Unless the injury is very severe, however, glomerular structures react quickly to injury by diffuse or focal cellular proliferation of the endothelial and epithelial cells of the capillaries or of Bowman's capsule of the glomerulus. Sometimes capillary endothelium, sometimes capsular epithelium shows the greatest amount of proliferation. Of the latter, that lining either the parietal or the visceral layer may show the greatest amount of proliferation. Proliferated

cells later may undergo degeneration or intercellular fibrils may appear, the latter more generally being considered to have been



FIG. 2.—Glomerulus from rabbit after uranium nitrate intoxication, showing similar proliferation of cells as in Figure 1, from Christian and O'Hare.³

formed by invading connective tissue cells. Thrombi may form within the capillary loops and subsequently organize. The base-

ment membrane of capillaries and of Bowman's capsule may undergo hyaline transformation or thicken. In this way a large variety of glomerular lesions can and do result, the variety depending on variation in degeneration and proliferation acting in a very complex structure, these changes primarily having resulted from injury to the glomerulus. What happens depends more on the degree than on the kind of the injury inflicted on the glomerulus.



FIG. 3.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 44,661, showing similar proliferation of cells as in Figure 1.

If what has just been stated is true, and I believe it is, we should find identical appearances in the glomeruli resulting from different injurious actions affecting the kidney. In other words, a high degree of non-specificity of glomerular lesions should be demonstrable. This has been recognized by many pathologists, although still there is a marked tendency to describe a given type of glomerular lesion as an index of a particular pathological process or disease and in that sense diagnostic. Apparently this idea is more prevalent

among clinicians than among pathologists. For this reason it seems worth while to emphasize the non-specificity of glomerular lesions.

Diffuse cellular proliferation in the glomerulus occurs in patients with acute or subacute glomerulonephritis (Bright's disease) with such frequency that we call a type of glomerulonephritis intracapil-



FIG. 4.—Glomerulus from a case of eclampsia, showing similar proliferation of cells as in Figure 1, from Dexter and Weiss.⁶

lary proliferative glomerulonephritis (Fig. 1). However, that same lesion is encountered, usually with much less frequency, in the kidneys of rabbits poisoned with uranium nephritis (Fig. 2). In man, in subacute *Streptococcus viridans* endocarditis, this is the glomerular lesion seen most frequently (Fig. 3). It is described in eclampsia (Fig. 4). In acute and subacute pyelonephritis¹⁰ it is frequent in certain stages of the progression of the process (Fig. 5).

Focal glomerular lesions consisting of epithelial cells proliferated from the parietal layer of Bowman's capsule, spoken of as epithelial crescents, are seen often in the kidneys of acute and subacute glomerulonephritis (Bright's disease) (Fig. 6), giving rise to the term proliferative capsular epithelial glomerulonephritis. Identical focal epithelial proliferation I have observed also in subacute *Streptococcus viridans* endocarditis (Fig. 7), in acute and subacute pyelonephritis and in uranium poisoning (Fig. 8). This form of

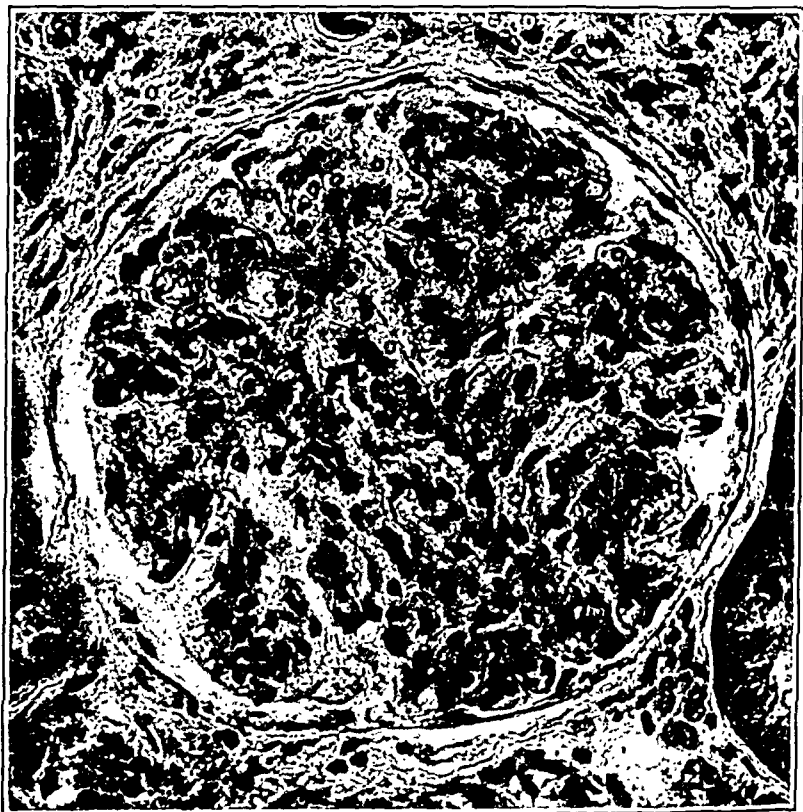


FIG. 5.—Glomerulus from a case of pyelonephritis, P.B.B.H., Path. No. 39,134, showing similar proliferation of cells as in Figure 1.

proliferative process may be focal, or it may extend so as to surround the capillary tuft more or less completely and result in a thickened capsule (Figs. 9 and 10). Cell degeneration and connective tissue proliferation may ensue, some of the lesions becoming fibrous, sometimes with much thickening of the fibrous part of the parietal layer of Bowman's capsule (Figs. 10 and 11).

Instead of, or in addition to the lesions already described, thrombi may be found in the capillaries of the glomerular tuft and undergo

varying changes. Extensively obstructing capillaries, they can cause degeneration and disorganization of glomeruli. This type of lesion has been associated particularly with subacute bacterial endocarditis (Figs. 11 and 13) and regarded by many as embolic lesions. In my own studies of this disease, this type of lesion was

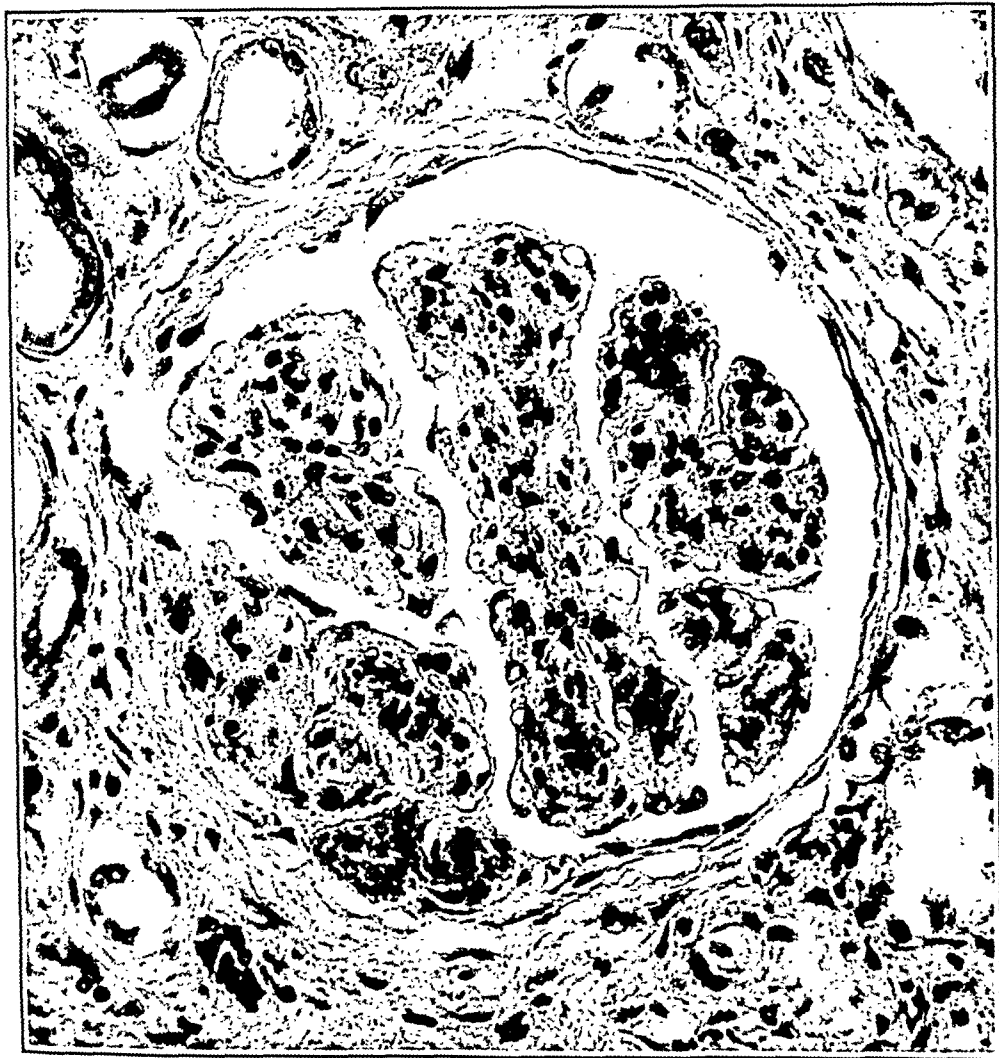


Fig. 6.—Glomerulus from a case of glomerulonephritis, P.B.B.H., Path. No. 25-127, showing focal cell proliferation, epithelial crescent.

not found to be particularly frequent, actually less frequent than other forms of glomerular lesion. As far as I could judge, the lesion usually was formed locally, although small embolic masses of bacteria may have lodged in the capillary to inaugurate the injury of the capillary wall which in turn caused the thrombus to form, and so they are thrombotic in the main rather than embolic lesions. This

view is supported by the frequent presence of identical lesions in the glomerular capillaries of experimental uranium nephritis (Fig. 12), particularly when the uranium has been injected into a peripheral or renal vein. Such glomerular thrombi have been noted also in

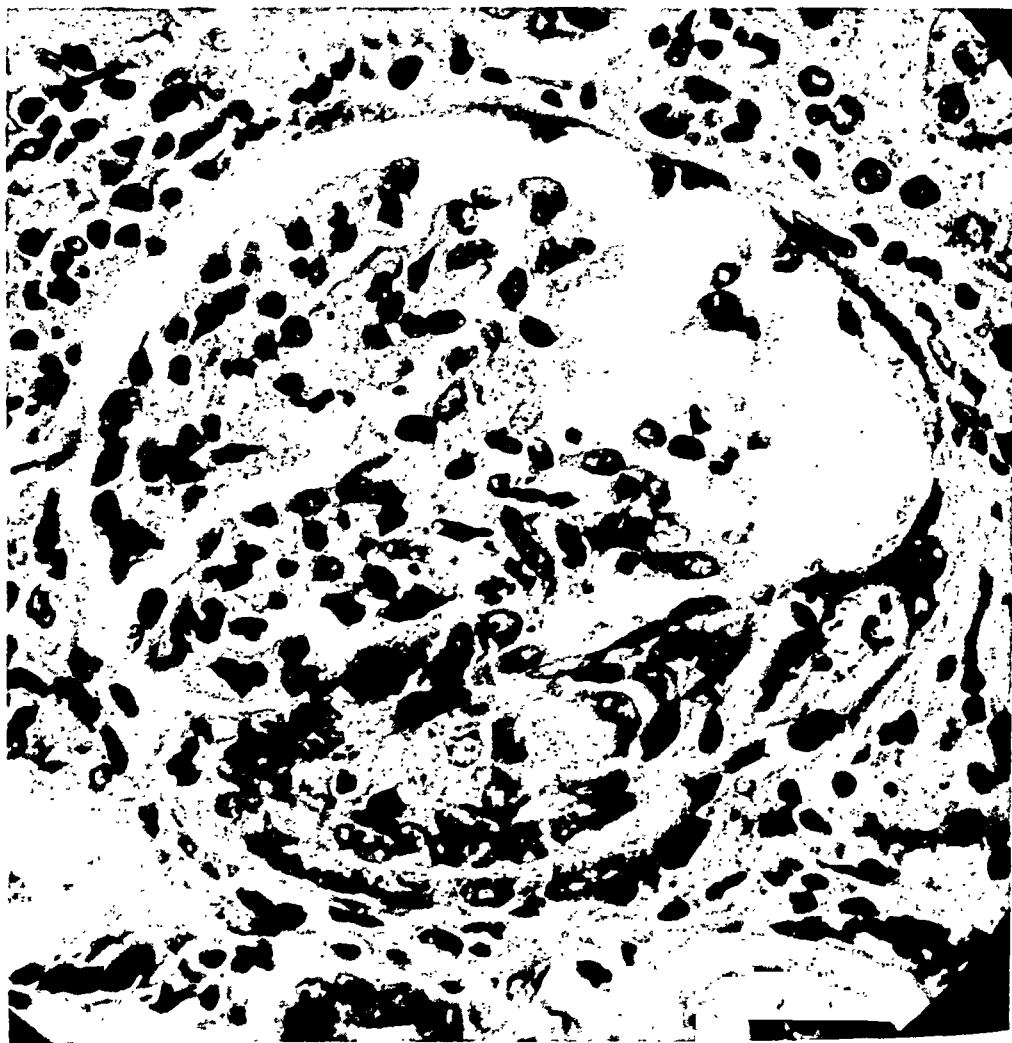


FIG. 7.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 26,400, showing similar focal cell proliferation as in Figure 6.

eclampsia (Fig. 14) and in acute and subacute nephritis and pyelitis. All of this indicates the non-specificity of glomerular lesions.

An intracapillary fibrous glomerular lesion has been described in a clinical syndrome of hypertension, diabetes mellitus and renal

insufficiency.^{8,9} Horn and Smetana⁷ pointed out that this is not limited to this syndrome (Fig. 15). I have described lesions like this in subacute *Streptococcus viridans* endocarditis (Fig. 16) and seen them in subacute glomerulonephritis (Bright's disease) and pyelonephritis.

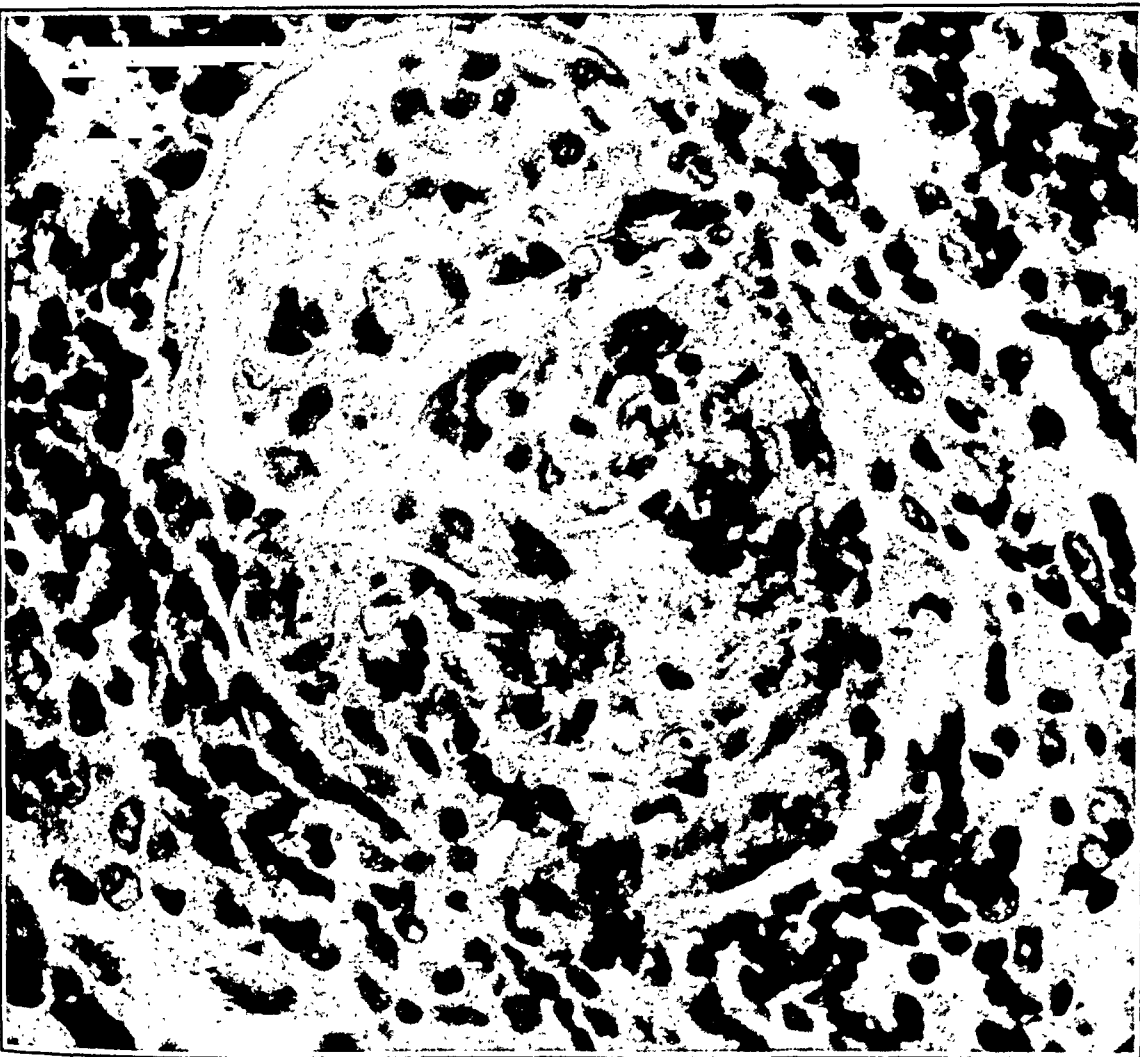


FIG. 8.—Glomerulus from rabbit after uranium nitrate intoxication, showing similar focal cell proliferation as in Figure 6, from Christian and O'Hare.³

Hyaline thickening of the basement membrane of the capillary wall has been observed in acute glomerulonephritis, in eclampsia and in subacute bacterial endocarditis, sometimes with duplication (Figs. 17 and 18).

As might be expected, when glomerular lesions become chronic, they show similar appearances, whatever the underlying condition may have been; glomeruli show various stages of atrophy and fibrosis

with their final disappearance. This explains why clinically an almost identical congerie of symptoms and signs are found irrespective of

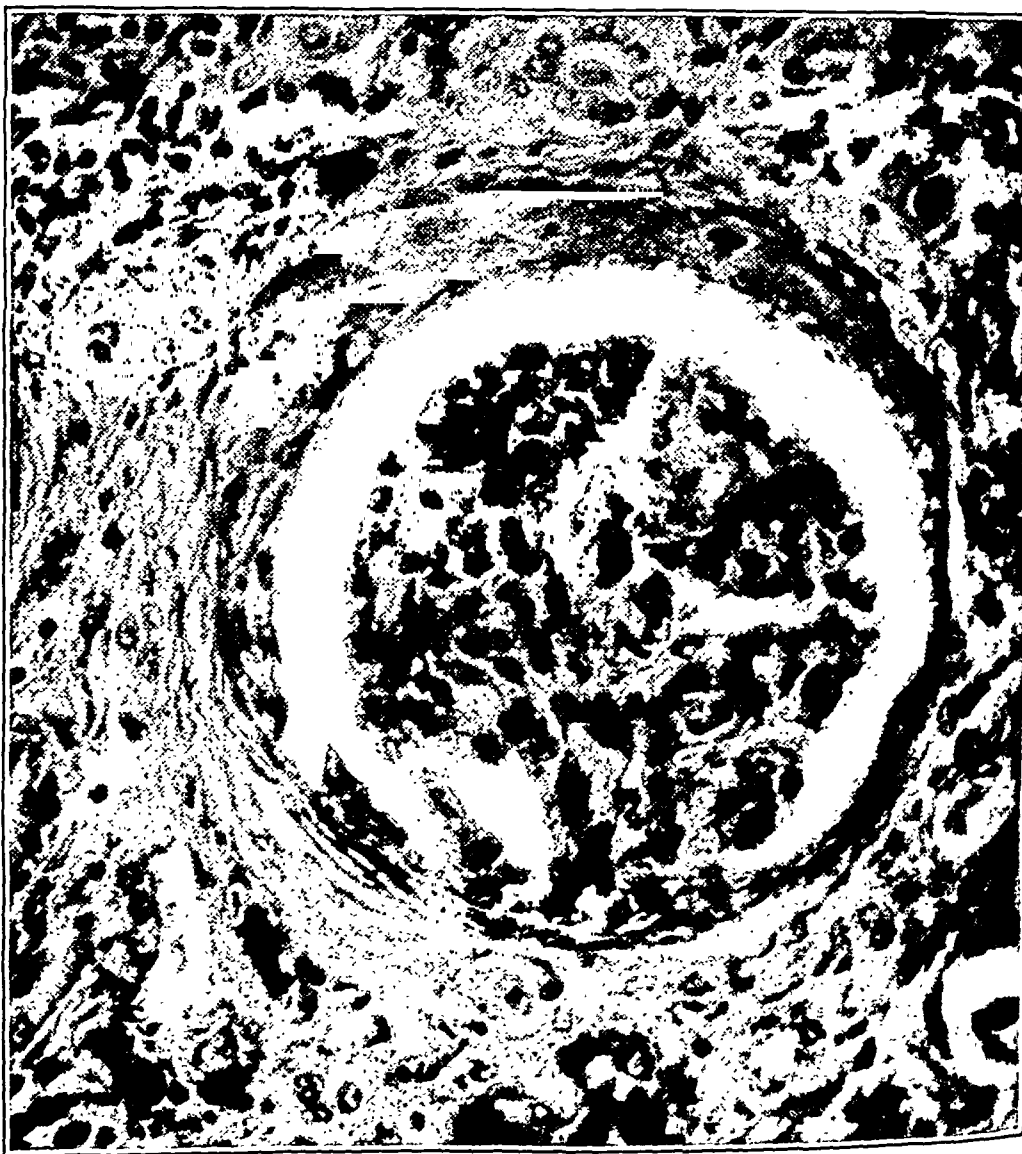


FIG. 9.—Glomerulus from a case of pyelonephritis, showing fibrous thickening of Bowman's capsule, from Weiss and Parker.¹⁰

whether the early stages of the process has been acute, then subacute glomerulonephritis or pyelonephritis or a progressive arteriolo-nephrosclerosis.

Other examples of non-specificity of glomerular lesions probably exist. However, those that I have cited, are sufficient to prove my thesis of their non-specificity.



FIG. 10.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 44,767, showing fibrous thickening of Bowman's capsule as in Figure 9.

Some 10 years ago I pointed out, under the title, "A Glomerular Dominance in Bright's Disease",⁵ how completely the clinical picture resulted from the changes which were going on in the glomeruli.

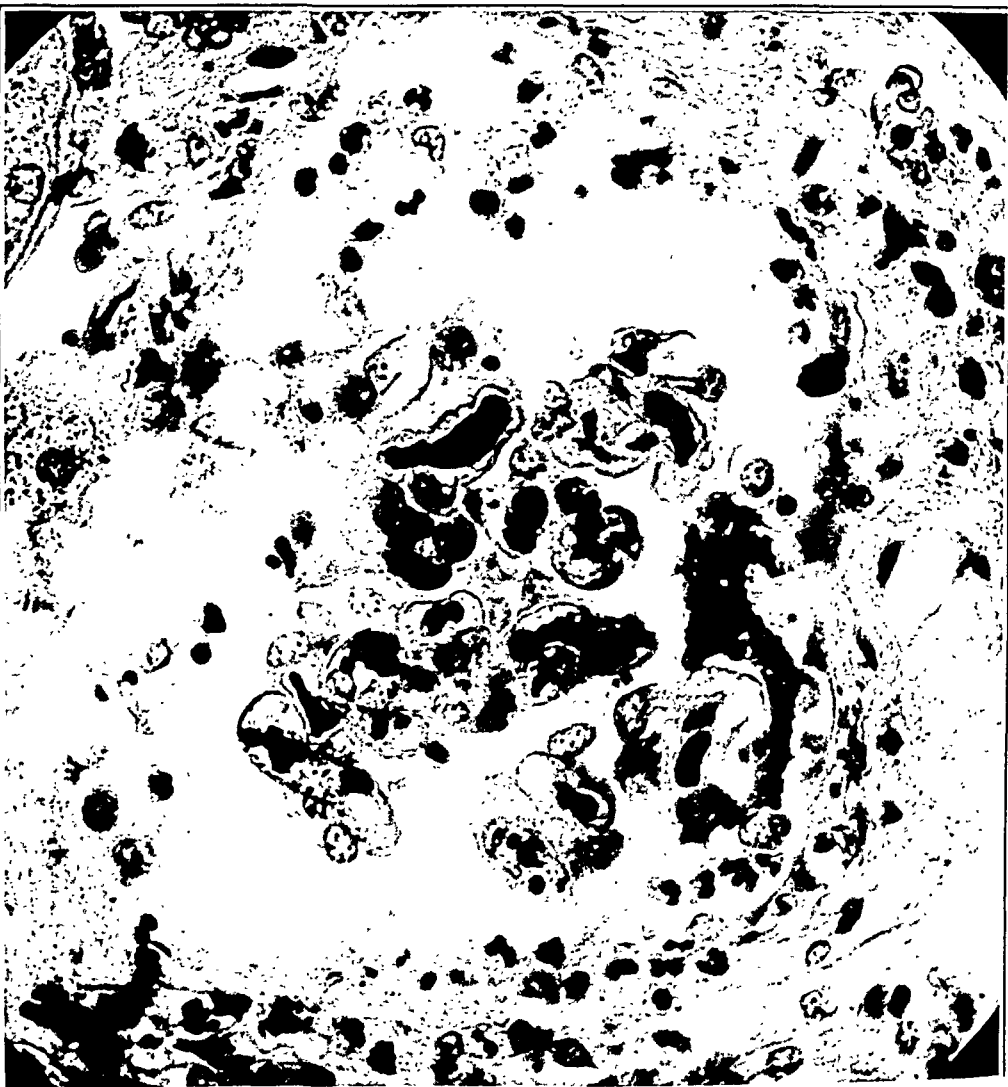
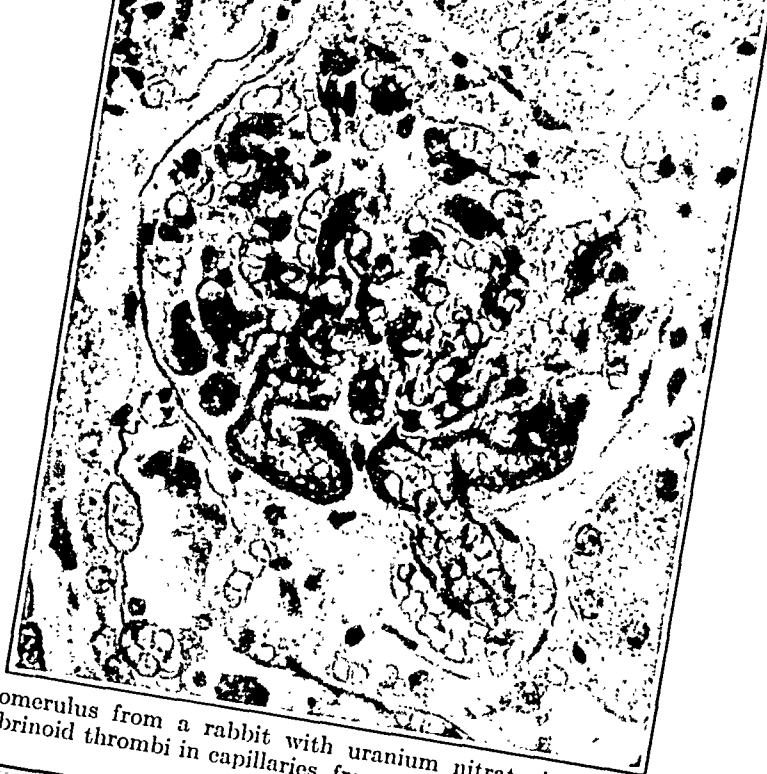


FIG. 11.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 49,045, showing fibrinoid thrombi in capillaries.

If signs and symptoms of renal disease depend so largely on lesions in the glomeruli, and if glomerular lesions are not highly specific, then it is not unexpected to find that many signs and symptoms are



g. 12.—Glomerulus from a rabbit with uranium nitrate intoxication, showing fibrinoid thrombi in capillaries, from Christian and O'Hare.³

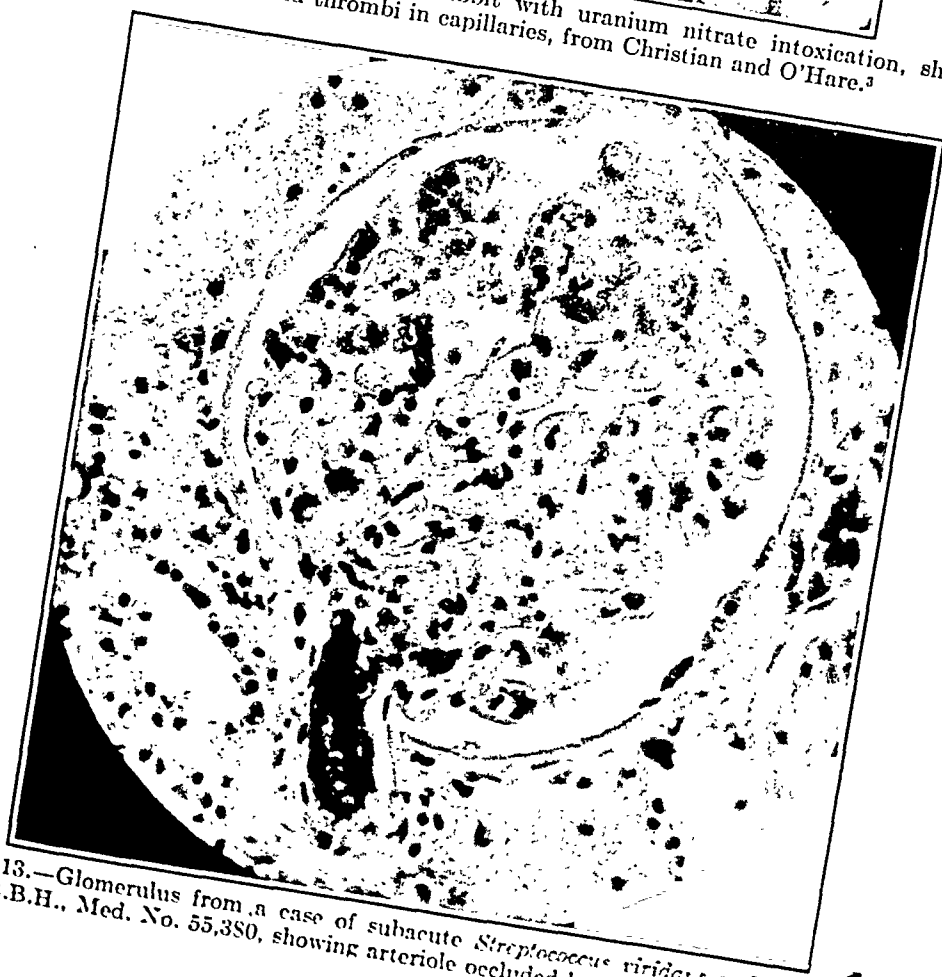


FIG. 13.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 55,380, showing arteriole occluded by a fibrinoid thrombus.

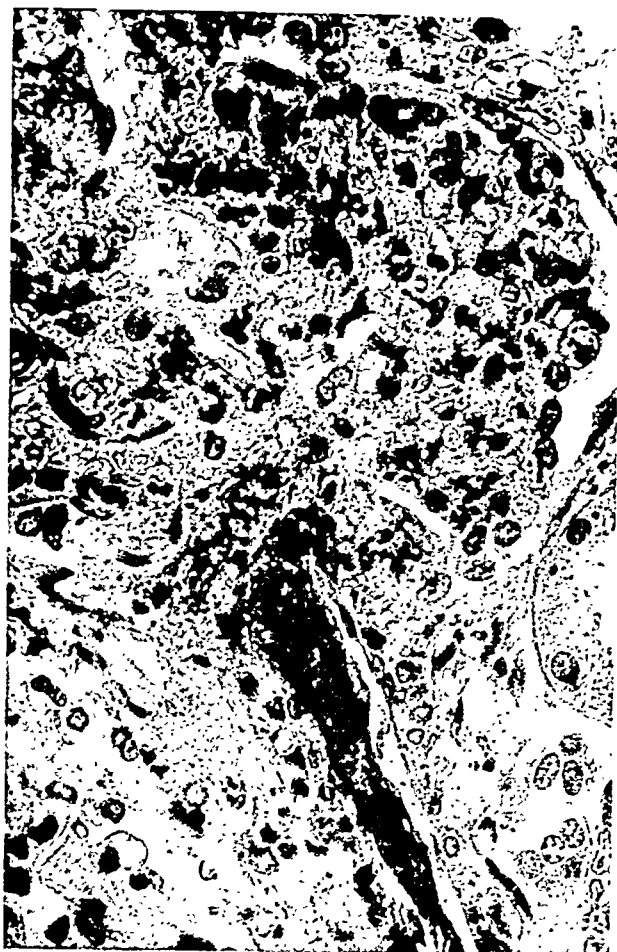


FIG. 14.—Glomerulus from a case of eclampsia, showing arteriole occluded by a fibrinoid thrombus, from Dexter and Weiss.⁶

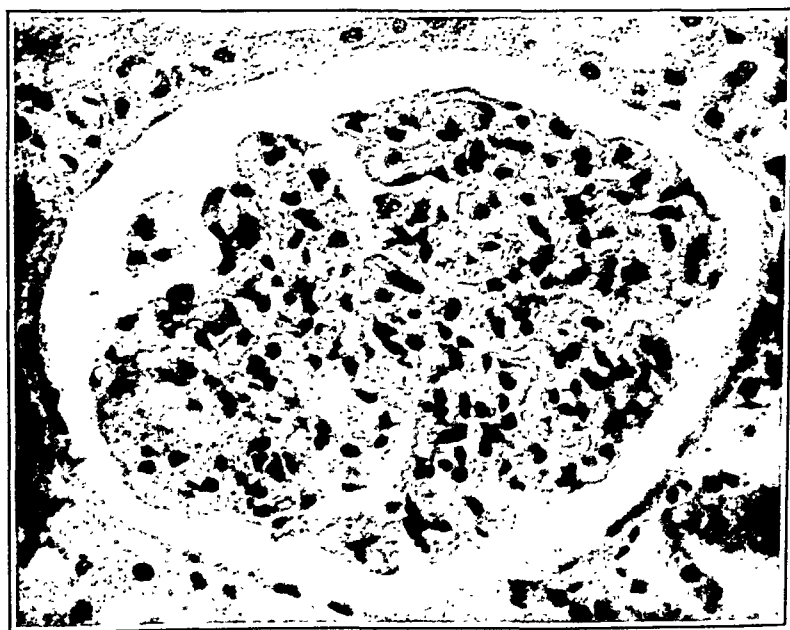


FIG. 15.—Glomerulus from a case of generalized arteriolar sclerosis without associated diabetes or renal disease, showing intercapillary glomerulosclerosis, from Horn and Smetana.⁷

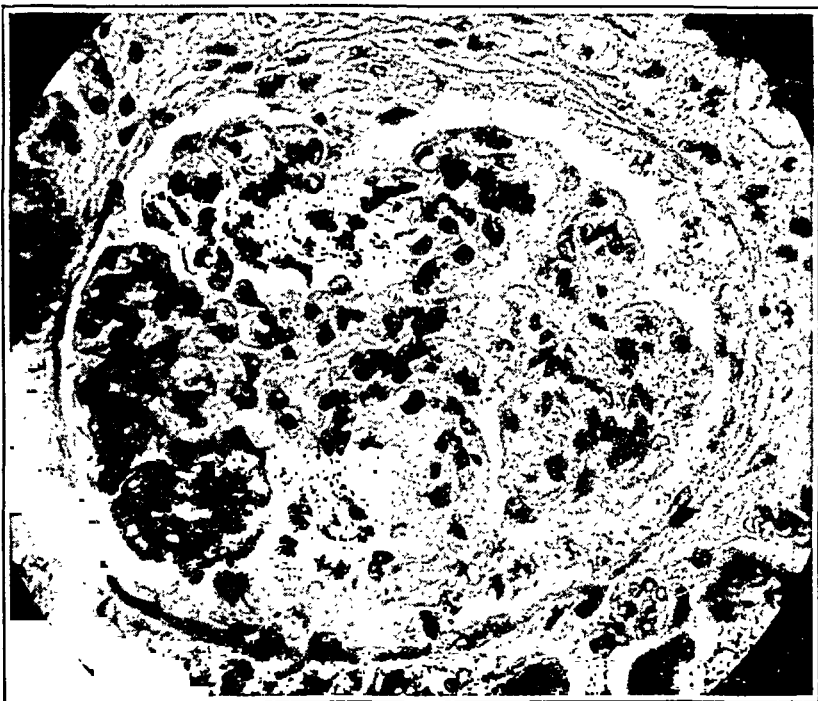


FIG. 16.—Glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 49,045, showing lesion similar to one in Figure 15.



FIG. 17.—Portion of glomerulus from case of eclampsia, showing hyaline thickening and duplication of basement membrane of glomerular capillary, from Dexter and Weiss.⁶

repeated in various conditions with acute, subacute and chronic renal lesions; this is just what we observe in the clinical study of our patients.



FIG. 18.—Portion of glomerulus from a case of subacute *Streptococcus viridans* endocarditis, P.B.B.H., Med. No. 55,380, showing hyaline thickening and duplication of basement membrane of glomerular capillary as in Figure 17.

Summary. This paper has emphasized the non-specificity of lesions observed in the glomerulus of the kidney and offers this non-specificity as an explanation of many similarities in the signs and symptoms of renal diseases.

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NON-SPECIFIC EFFECT OF CERTAIN KIDNEY EXTRACTS IN LOWERING BLOOD PRESSURE

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RECENT advances in the knowledge of the humoral mechanism of hypertension have suggested a new avenue for the treatment of arterial hypertension. Following Goldblatt's observations on the relation of renal ischemia to hypertension, animals which had this type of hypertension were treated with renal extracts, and a decrease in arterial pressure was observed.^{3,7,8} Arterial hypertension in man also has been treated with kidney extracts and favorable results have been reported.^{3,7,8} The question immediately arises whether the renal extract specifically inactivates the renin-hypertensin system which has been postulated to be the mechanism by which renal ischemia produces hypertension, or whether the fall in arterial pressure is the result of a generalized toxic effect of a crude tissue extract on the cells of the body. In an attempt to answer this question, kidney extracts were prepared and injected parenterally into patients with arterial hypertension.

Method. *Preparation of the Renal Extract.* Though the kidney extract administered was probably identical with that prepared with the aid of heat by Page and his co-workers,⁷ to avoid confusion a short description is given of our method of preparing the extract used.

Fresh hog kidneys were ground in an electric meat chopper, first through a coarse and then through a fine sieve. Ten kilograms of the fine material were added to a solution of 300 ml. of glacial acetic acid and 300 gm. of sodium chloride in 15 l. of water. The vessel containing this material was then immersed in a water bath maintained at about 65° C., and the mixture stirred mechanically. It reached a temperature of 56° C. after 20 to 30 minutes and was kept at this temperature for 15 minutes. It was then filtered by gravity and yielded between 16 and 17 l. of a clear yellow filtrate in 2 to 4 hours. To each liter of filtrate 740 gm. of ammonium sulphate were added while stirring. The material was then left overnight at room temperature. The precipitate was collected on Buechner funnels and dissolved in cold water. The volume was then brought to 9000 ml. with cold water. The ammonium sulphate concentration was determined by nesslerization, and enough solid ammonium sulphate (420–470 gm. per l.) was added to obtain a solution 75 to 80% saturated with ammonium sulphate. This mixture was again kept overnight at room temperature. The precipitate was removed by suction through a layer of Hyflo Filter Aid and redissolved in cold water. The volume was brought to 6000 ml. with cold

water. The Hyflo Filter Aid was removed by suction through Whatman No. 50 filter paper, and the ammonium sulphate concentration of the clear filtrate was determined by nesslerization. Again, enough solid ammonium sulphate was added to produce a solution 80% saturated. After standing overnight at room temperature the precipitate was collected on Buechner funnels over a layer of Hyflo Filter Aid and taken up in 60 to 100 ml. of cold water. The resulting thin paste was placed in a cellophane bag and dialyzed against distilled water at 1° C. In order to remove all ammonium sulphate the dialysis had to be continued for about 5 days, during which time the distilled water was renewed daily and the contents of the dialyzing bag mixed thoroughly once every day. The extract was then freed from the Hyflo Filter Aid by suction, and the filtrate was concentrated *in vacuo* at temperatures below 50° C. to a volume of 100 to 130 ml. The concentrate obtained was filtered first through a coarse and then through a fine Pyrex sintered glass filter. Sodium chloride was added (0.85 gm. per 100 ml.) and filtration through a Seitz filter was carried out. Sterility was controlled by aerobic and anaerobic cultures of each batch after the filtrate had been transferred to rubber stoppered vaccine bottles.

Properties of the Extract. One ml. of the final product was obtained from 75 to 100 gm. of hog kidneys. The extract contained 2.5 to 4.8 gm. of nitrogen per 100 ml. Only 16 to 28% of this nitrogen was present in the form of proteins (pseudoglobulins), while the rest existed in the form of proteoses, soluble in trichloroacetic acid, but precipitated by ammonium sulphate and by picric acid. All extracts contained renin, the concentration being between 180 and 250 rabbit units per ml., as determined by the method of Schales and Haynes.⁹ The extracts had diastatic activity; 100 ml. produced an amount of reducing material equivalent to 0.4 to 1.1 gm. of glucose from an excess of starch in 30 minutes at 37° C. and pH 6.8. The hypertensinase content of the extract was estimated by incubation with angiotonin (hypertensin) solutions at pH 7.4 for 2 hours. The destruction of angiotonin was determined by comparing the effect of such a mixture (after removal of proteins) on the arterial blood pressure of an anesthetized cat with that of a blank in which water instead of extract had been incubated with angiotonin. The hypertensinase activity of the extracts was such that 1 ml. inactivated *in vitro* the amount of angiotonin produced by incubating from 1 to 3 l. of beef serum with an excess of renin under optimal conditions.

In several extracts a major portion of the hypertensinase was destroyed by incubating for 9 hours at 37° C. and pH 3.7. While this treatment should, according to Fasciolo and his co-workers,² inactivate all hypertensinase present, experiments in our laboratory showed that only about 90% of the hypertensinase had been destroyed. It is probable that the extracts contain not only the hypertensinase active at pH 7.4, which Fasciolo states is inactivated by standing at room temperature and pH 3.6 to 3.9 for 30 minutes, but also a second enzyme not destroyed by this treatment. The presence in kidney extracts of such a "second hypertensinase"

with an optimum for the destruction of angiotonin at pH 4 has been recently described.⁶ This enzyme will not be inactivated by keeping the pH of its solution at pH 3.7.⁵

Injection of Renal Extracts into Patients with Arterial Hypertension. The effect of the kidney extract was studied on 7 patients. All the patients were admitted to this hospital, but remained ambulatory throughout their hospitalization. The extract was injected intramuscularly in the buttock, except on a few occasions when it was given intravenously. The blood pressure readings were made twice daily by one of the authors; and the value appearing on the charts is the average of these readings. Temperatures were recorded at least 4 times daily and that recorded on the charts is the highest daily value. The severity of the local reactions was graded from 1+ to 4+, depending on the amount of induration, erythema, and tenderness. Roentgen ray examination of the heart, electrocardiograms, blood and urine studies on these subjects were obtained at various times throughout their hospital course.

Case Abstracts. CASE 1, a 46-year-old male, had apparently been well until 3 to 4 months prior to admission, when he developed progressive difficulty with vision, headaches, dyspnea, and weight loss. On admission to the hospital, physical examination revealed marked retinal changes with tortuous, irregular vessels, hemorrhages and exudates. The heart was slightly enlarged, but the lungs were clear. Blood pressure at this time was 250/140 mm. Hg and remained at about this level. Laboratory studies revealed anemia, albuminuria, hematuria, and cylindruria. The renal function was depressed, and the blood urea nitrogen rose as high as 160 mg. per 100 cc. During his hospital course he developed evidence of cardiac failure and hypertensive encephalopathy. The diagnosis of rapidly progressing malignant hypertension with cardiac and renal failure was made.

After several weeks in the hospital, during which time his blood pressure remained stable, therapy with the renal extract was begun. He received daily intramuscular injections of 10 cc. of the extract for a period of 2 weeks. There were neither local reactions, constitutional symptoms, nor any change in blood pressure. In addition to the intramuscular injections, the patient received 3 intravenous injections of kidney extract (2, 5, and 10 cc.) without any reaction or depressor effect. His course continued progressively downhill, seemingly uninfluenced by the injections, and he died March 7, 1942. Autopsy confirmed the diagnosis of malignant hypertension.

CASE 2, a 42-year-old salesman, was apparently well until 1 year before admission, when in a routine life insurance examination he was found to have an arterial pressure of 200/130 mm. Hg. Soon after this he developed dull, early-morning headaches and nocturia, followed later by paroxysmal respiratory distress, orthopnea, and edema. In November 1941 he was admitted to this hospital. Physical examination on entrance revealed marked retinal vascular sclerosis with hemorrhages and exudates, an enlarged heart, and slight ankle edema. His blood pressure at this time was 220/130 mm. Hg. Laboratory studies showed a moderate anemia, albuminuria, microscopic hematuria, and cylindruria. The diagnosis of malignant hypertension with cardiac and renal failure was made.

The patient received 21 injections of 10 cc. each of kidney extract intramuscularly. There were only minimal local reactions, no constitutional symptoms, and no change in his arterial pressure. During a later hospital

admission he received an injection of 1 cc. of kidney extract intravenously, which was followed by a severe chill reaction, but was without effect on the arterial blood pressure.

CASE 3, a 31-year-old single female, had been well until 6 months prior to admission when she began to "lose pep" and fatigue easily. Later she developed blurred vision, headache, and occasional nausea and vomiting. In December 1941, when she entered this hospital, physical examination revealed marked retinal changes with papilledema, vascular sclerosis, hemorrhages and exudate. The heart was slightly enlarged, and the blood pressure was 250/160 mm. Hg. There was moderate anemia, marked albuminuria, and depressed renal function. The diagnosis made was rapidly

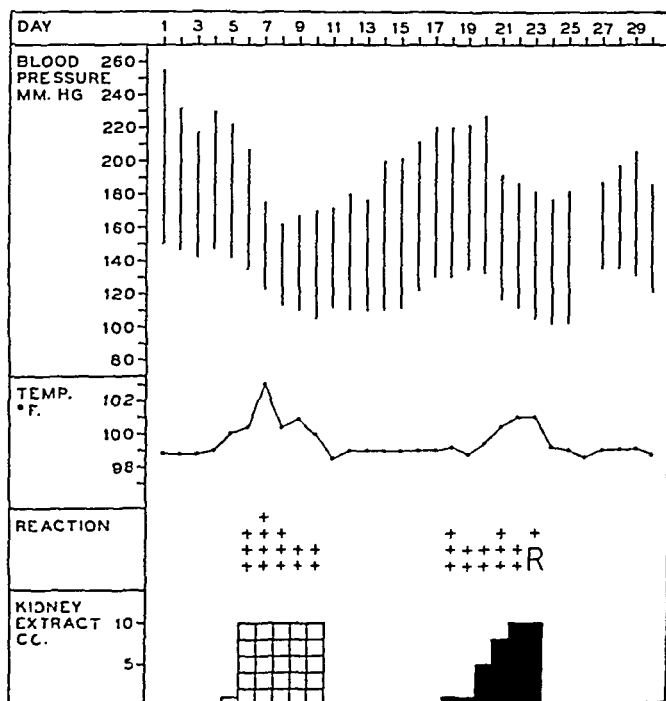


CHART 1.—Data of Case 3. In this and the following charts, dosage of unmodified renal extracts shown by white squares; dosage of hypertensinase-poor extract by the black blocks. The local reactions are graded from 1+ to 4+, depending on their severity. Shocklike reactions are indicated by *R*.

progressing malignant hypertension. During this admission she received several injections of kidney extract. Although the dose never exceeded 5 cc. per injection, there were marked local reactions with induration, erythema, and pain. There was a definite decrease in the blood pressure at this time, but because the reactions were so severe, injections were discontinued and she was discharged from the hospital.

In April 1942, the patient was readmitted for further injections. The findings on physical examination and laboratory data were unchanged from the previous admission. She received 5 intramuscular injections of 10 cc. each (Chart 1), all of which were followed by moderately severe local reactions consisting of redness, induration, heat, and tenderness at the injection site. Weakness, anorexia, and marked sweating developed.

These reactions were accompanied by a definite decline in arterial pressure. The patient remained in the hospital after therapy was stopped, and her blood pressure rose gradually almost to its former level. Injections with hypertensinase-poor extract were then started. This therapy produced severe local and systemic effects, and the arterial pressure again fell. The patient complained of generalized arthralgia. She experienced one severe shocklike reaction with a marked fall in blood pressure. Therapy was again stopped, and the arterial pressure once more rose gradually.

CASE 4, a 35-year-old housewife, had an episode of dysuria and bloody urine 13 years previous to the present admission. Six years before the present admission she was first found to have high blood pressure and albuminuria. During her first admission to this hospital 4 years ago, her blood pressure was recorded at 190/103 mm. Hg. In the intervening time she developed blurred vision, increasing weakness and pallor and severe retinal damage with papilledema, vascular sclerosis, hemorrhages, and exudate. The heart was enlarged, and the average blood pressure was 260/150 mm. Hg. There was a mild anemia, albuminuria, and moderately diminished renal function. The diagnosis of moderately rapidly progressing malignant hypertension was made.

Following a period of observation, injections of kidney extract were instituted. An injection of 1 cc. of kidney extract intravenously was followed by a severe chill and febrile reaction (Chart 2). A moderate diminution of blood pressure occurred. Thereafter therapy consisted of daily intramuscular injections of 10 cc. of the extract. After the seventh injection there was a severe local reaction with fever, chilly sensations, sweating, and malaise. With this type of response there was a drop in her blood pressure (Chart 2). There was no definite change in the physical findings or laboratory data during the period of diminished blood pressure. After 18 days of treatment, the injections were stopped, and the blood pressure slowly rose to pre-injection levels. Intramuscular injections of hypertensinase-poor extract were then given. These were followed by even more severe local and systemic reactions. There was a striking decrease in the arterial pressure. The eighth injection produced a very severe shocklike reaction with imperceptible blood pressure. The injections were again stopped, and the blood pressure rose rapidly to its previous levels.

CASE 5, a 33-year-old married housewife, had had a pregnancy 9 years previously, which had been complicated by pyelitis, hypertension, and edema. Since that time she had been known to have a slightly elevated blood pressure. Two later pregnancies were complicated by hypertension and albuminuria. During the 4 years preceding admission she experienced increasing symptoms of breathlessness, headache, and fatigue. Her blood pressure on repeated visits to the out-patient clinic had averaged about 220/120 mm. Hg. Physical examination on admission to this hospital in March 1942 revealed moderate retinal sclerosis, but no hemorrhage or exudate. The heart was slightly enlarged, and there were râles at both lung bases. Laboratory data revealed only a moderate albuminuria and many white blood cells in the urinary sediment. Renal function was good, and there was no nitrogen retention. A diagnosis of rather severe essential hypertension, possibly caused by chronic pyelonephritis, was made.

Following a period of observation, the patient received daily an injection of 10 cc. of kidney extract in the muscles of the buttock (Chart 3). After the fifth injection severe local and systemic reactions appeared. A moderate fall in arterial pressure developed. After about 3 weeks the therapy was discontinued, and the blood pressure slowly rose to its original level. Therapy with hypertensinase-poor extract was then instituted and was followed by severe local and general reactions. There was a decrease in

blood pressure, just as there had been with the original extract. And similarly, a few days after the last injection the arterial pressure again rose to its previous level.

CASE 6, a 52-year-old housewife, was known to have had hypertension of at least 6 years duration. Eighteen years prior to admission there had been a pregnancy with albuminuria and edema, but no known hypertension. The presence of hypertension was established 6 years before, when, suffering from edema and dyspnea, she was admitted to the medical wards of this hospital. Since that time she had been followed in the out-patient clinic, and her blood pressure had averaged about 250/140 mm. Hg. She was readmitted to the hospital in January 1942 because of a recurrence of her symptoms, and physical examination at this time revealed a slightly orthopedic woman. Her retinal vessels were tortuous with arteriovenous nicking,

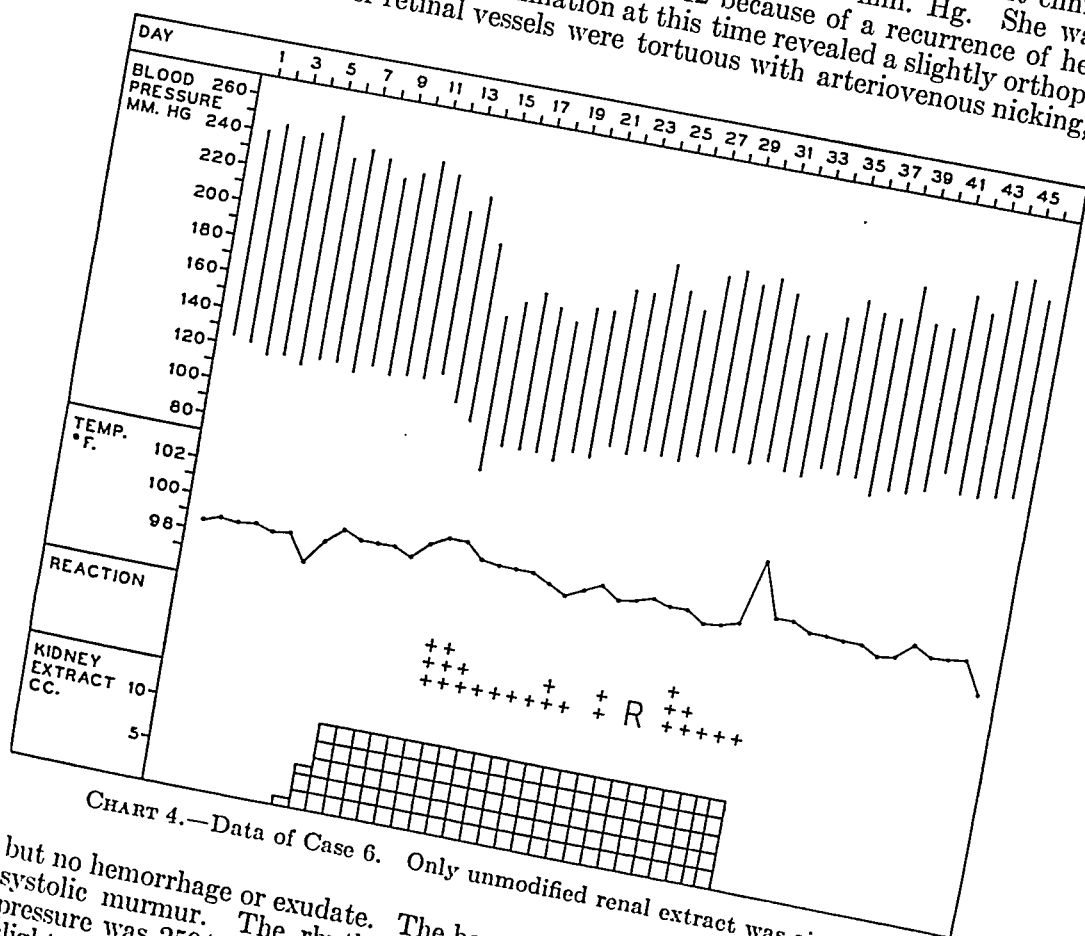


CHART 4.—Data of Case 6. Only unmodified renal extract was given.

but no hemorrhage or exudate. The heart was enlarged with a slight apical systolic murmur. The rhythm was absolutely irregular, and the blood pressure was 250/140 mm. Hg. There were râles at both lung bases and slight peripheral edema. There was no anemia or nitrogen retention; but there was slight albuminuria. Roentgen examination revealed moderate cardiac enlargement, and an electrocardiogram showed auricular fibrillation and left axis deviation. The diagnosis of long-standing, benign hypertension with mild cardiac failure was made.

After several weeks in the hospital the state of her circulation improved, and intramuscular injections of kidney extract were instituted (Chart 4). Following the eighth injection there was a marked local reaction with induration, erythema, and pain. This was associated with weakness, mild fever, and sweating. There was an abrupt decline in arterial pressure at this time. With subsequent injections, the reactions continued with vary-

ing degrees of severity, but despite this her blood pressure rose to almost its former level. On the twentieth day of therapy she had a severe, shock-like reaction. Following the twenty-sixth injection there was an extremely severe and long-lived local reaction, and the injections were thereupon discontinued. Her blood pressure remained elevated throughout the remainder of her hospital course. There was no significant change in retinae, heart size, electrocardiographic findings, or laboratory data, either at the time of maximal response or when the injections were discontinued.

CASE 7, a 53-year-old married housewife, had been known to have a markedly elevated blood pressure for about 15 years. On repeated visits to the out-patient clinic of this hospital she had been found to have a blood pressure averaging about 230/130 mm. Hg. Her only complaint had been moderate headaches, except that she had experienced occasional attacks of

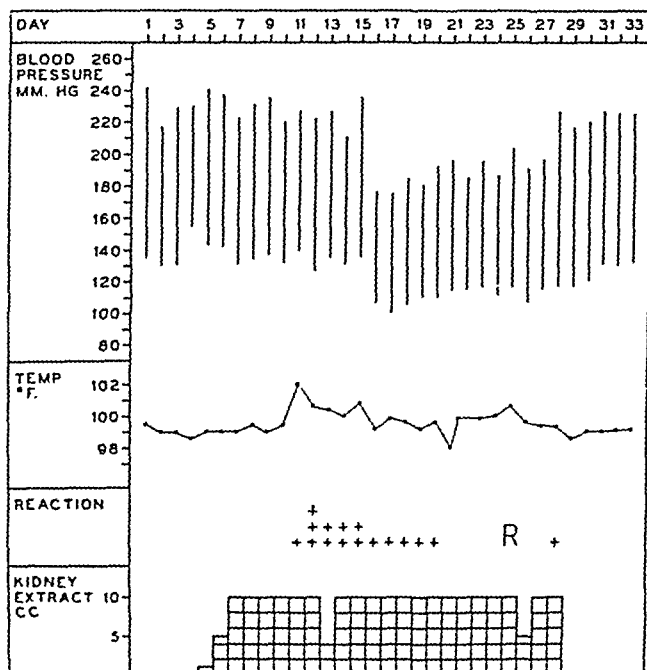


CHART 5 —Data of Case 7. Only unmodified renal extract was given.

nausea, vomiting, and abdominal pain thought to be due to cholelithiasis. During recent years there had been mild dyspnea on exertion. She was admitted to the hospital in March 1942 for therapy with kidney extract. Physical examination at that time showed marked variation in the caliber of the retinal vessels with arteriovenous nicking, several small hemorrhages, but no exudates. The heart was enlarged and the average blood pressure at this time was 250/135 mm. Hg. Laboratory data showed only a mild anemia, and electrocardiograms revealed only left axis deviation. The diagnosis was "benign" hypertension of very long standing.

Following a period of observation the patient received extract intramuscularly (Chart 5). After about 1 week of therapy local reactions with erythema, induration, and tenderness appeared accompanied by fever, sweating, and malaise. Soon after this her pressure showed a definite decrease. The injections were continued daily, yet the blood pressure

slowly rose to its previous level. There was one severe, shocklike reaction with a precipitous fall in blood pressure. Following her twenty-third and twenty-fourth injections severe urticaria appeared, and no further injections were given. There was no change in the patient's condition, or in the findings on physical examination or laboratory data except that she developed an increased anemia while receiving the injections.

Summary of Clinical Observations. Of the patients receiving the kidney extract, 4 had malignant hypertension and 3 had a more chronic or benign variety. The patients, of whom 5 were females and 2 males, ranged in age from 31 to 53 years.

In 2 patients (Cases 1 and 2), both males with malignant hypertension, the extract was given in full dosage (10 cc. per dose) intramuscularly over periods of 2 and 3 weeks. The blood pressure in neither showed significant variation, nor was there any definite symptomatic change. Other than very minimal soreness and induration at the site of injection, no local or systemic reactions occurred. Both of these patients also received extract intravenously. In one, a severe chill reaction followed the injection of 1 cc. of extract intravenously, but there was no change in blood pressure. No further injections were given to this patient. The other patient received intravenous injections of 2, 5, and 10 cc. without any reaction. His arterial pressure remained unchanged.

In the remaining 5 patients the daily intramuscular injection of kidney extract produced a significant decline in arterial pressure. The initial injections were followed by slight tenderness and pain at the site of injection, but there were no other symptoms until after the injections had been continued daily for from 2 to 10 days. Then a different and more severe type of reaction occurred. After several hours the site of injection was surrounded by an area of marked induration which usually involved the entire buttock and frequently spread over the sacral and lumbar regions. The skin was red and hot, and in many cases an erythematous confluent macular eruption occurred, which involved not only the skin of the injected buttock but also the skin over the sacrum and that of the lateral and anterior aspects of the thigh where there was a bandlike area of erythema parallel to and just below the inguinal ligament. Associated with this severe type of local reaction, there were various constitutional symptoms of fever, chilliness, sweating, anorexia, and lethargy. The maximum fever was usually reached about 6 hours after injection, and then declined to normal within 12 to 24 hours. Associated with this type of response there was a definite decrease in the arterial blood pressure (Charts 1-5).

As long as the injections were given, the patients continued to have constitutional symptoms and local reactions of varying severity. Weakness, sweating, and loss of appetite appeared to be out of proportion to the febrile reaction. At times the patients appeared to have fewer headaches, but in general there was no striking change in their symptoms. The eye grounds showed no change. The heart

size and electrocardiograms were not affected. In some cases a moderate anemia developed, and in one case eosinophilia was noted. Leukocytosis did not appear. The sedimentation rate was elevated before therapy was started in most instances, and remained so throughout the period of injections. Urinalyses and kidney function tests showed no striking change after therapy. In one patient the arterial pressure rose to its former level despite continued therapy.

After about 3 weeks of injection therapy new manifestations appeared. Particularly violent local reactions occurred, with induration that persisted for weeks. In 2 patients severe urticaria appeared a short time after injection, and in others a mild arthralgia occurred. Severe shocklike reactions occurred in 4 patients on one occasion each. These developed almost immediately after completion of the injections and were characterized by flushing of the face and a precipitous drop in arterial pressure. In these instances the patient complained of a feeling of warmth and of a tingling sensation in the fingers. After a short period of time extreme pallor developed; the pulse became rapid and feeble; and at times the arterial pressure was unobtainable. The patient complained of substernal pressure and "tightness" in the chest, but there was no evidence of bronchial spasm. There were some complaints of excruciating lumbar pain. In addition confusion, nausea, vomiting, diarrhea, and hoarseness occurred in several instances. The more severe part of the reaction passed within an hour, but the patient remained weak, hoarse and prostrated for the remainder of the day. Electrocardiograms failed to reveal evidence of myocardial infarction. The site of injection showed less reaction on the days that such severe shocklike reactions occurred.

After varying periods of time, the injections were stopped and the patients remained in the hospital, ambulatory as before. The weakness, sweating, and anorexia disappeared. The blood pressure in all cases gradually rose, within 2 weeks, to the pre-injection level.

A hypertensinase-poor renal extract was then prepared and in 3 patients therapy was resumed. These injections resulted immediately in marked local reactions, accompanied as before by constitutional symptoms, and by the sixth day all 3 patients had a definite decline in the arterial blood pressure. The local and systemic reactions were similar to those produced by the original extract. After a definite fall in blood pressure was obtained the injections were stopped, and with cessation of therapy the blood pressure tended to return to the initial levels.

Comment. The results obtained with the unmodified kidney extracts were similar to those reported by Page and his colleagues.⁴ The material was prepared by comparable methods and it was given in equivalent dosage. The severe shocklike reactions were like those reported by Page. Grollman, Williams and Harrison⁵ have reported

also that renal extracts cause a lowering of the arterial pressure in both human and experimental hypertension. These authors have administered crude renal extracts by both oral and parenteral routes. In their recent work they have used the dialyzable portion of the crude extract.⁴

It is well known that the arterial pressure in hypertensive patients may be lowered by febrile diseases. Stead and Kunkel¹⁰ reported striking decreases in arterial pressure in 2 hypertensive subjects treated with malaria. Chasis, Goldring and Smith¹ have observed that various pyrogenic agents, such as pyrogenic inulin, triple typhoid vaccine and tyrosinase, cause a fall in arterial pressure in hypertensive subjects. The fall in arterial pressure induced by these methods occurred also when the febrile reaction was prevented by the use of amidopyrine. The above authors state that injection of tyrosinase did not produce a fall in blood pressure until local reactions with fever occurred. The local reactions with constitutional symptoms which follow the repeated injection of tyrosinase were similar to those produced in our patients by the injection of renal extract.

In 5 of the 7 cases of arterial hypertension, the renal extract caused a definite decrease in arterial pressure. It is significant that no decrease occurred in the 2 patients who had no local reactions or constitutional symptoms. In the other 5 patients, the extract produced severe local reactions which were accompanied by constitutional symptoms. From the time that the arterial pressure began to fall the patients were obviously sick. Although the prostration that occurred in these patients was similar to that seen in patients recovering from a chill produced by the intravenous injection of typhoid vaccine, severe chill and high fever never occurred after the intramuscular injection of the kidney extract. A moderate rise in temperature usually developed at the time of the original fall in arterial pressure, but the weakness, sweating, and anorexia were much more pronounced than that usually seen with this degree of febrile reaction. Though there appeared to be a definite relationship between the fall in arterial pressure and the occurrence of severe local reactions and constitutional symptoms, there was no definite correlation between a sustained fall in arterial pressure and the severe shocklike reactions.

Daily observation of these patients led us to believe that the fall in arterial pressure was produced by a non-specific toxic effect of the renal extract on the body. It was impossible to distinguish between symptoms produced by the direct pharmacologic action of the tissue extract and those produced by the sensitization of the body to the extract. Certain of the signs and symptoms were undoubtedly allergic in origin, and the fact that the fall in arterial pressure did not usually occur until after several injections had been given

suggests that sensitization of the body to the extract may have played an important part in lowering the arterial pressure.

Two experiments were devised to determine whether the hypertensinase present in the extract was responsible for the fall in arterial pressure. First, the intravenous injection of the extract was attempted. In all but one instance sufficient quantities of the extract could not be given intravenously because of the chill reaction. One patient, however, received 10 cc. of the extract intravenously without a febrile reaction and without any change in blood pressure. This was taken as presumptive evidence that the hypertensinase in the daily dose of the extract was not capable of lowering the arterial pressure. The second approach was an attempt to destroy the hypertensinase in the extract, and then determine whether the extract still lowered the arterial pressure. The extract in which most of the hypertensinase had been destroyed was found to be as effective in lowering the arterial pressure as the original extract had been. These experiments served to confirm our belief that the decrease in arterial pressure was produced by a non-specific effect of the extract on the body rather than by specific interference with a renin-hypertensin reaction system.

Summary and Conclusions. 1. A kidney extract, similar to that of Page *et al.*, was prepared. The diastatic activity and the nitrogen distribution of the extract were determined chemically. The renin and hypertensinase activity were determined by biologic assay.

2. Seven patients with arterial hypertension were given daily intramuscular injections of the extract. In 5 of these patients there was a significant lowering of the arterial pressure, which appeared to be related to the fever, sweating, weakness, anorexia, and severe local reactions which were produced by the injections.

3. The arterial pressure was not lowered in 2 patients in whom injection of the extract produced neither local reactions nor constitutional symptoms.

4. Hypertensinase-poor extracts were prepared to determine whether the fall in arterial pressure was produced by the specific action of the hypertensinase on a renin-hypertensin system. Injection of these hypertensinase-poor extracts produced a fall in arterial pressure similar to that produced by the unmodified extract.

5. It is concluded that the decrease in arterial pressure was produced by a non-specific effect of the renal extracts on the body rather than by specific interference with a renin-hypertensin system.

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HORMONE EFFECTS ON THE MALE GASTRODUODENAL MUCOSA

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IN a recently published review¹ of 444 cases of gastric carcinoma, we called attention to the age incidence and sex discrepancy in this condition, and suggested an endocrine basis. The new field of inquiry opened to gastro-enterologists by the recently isolated and synthesized sex hormones also was pointed out.

In an effort to correlate the marked changes in the content and character of the sex hormones which take place during that period when gastric carcinoma is most prevalent with the effects of age and sex on the physiology and pathology of the gastric mucosa, we reviewed those cases of benign gastroduodenal lesions which we had available. In the past 15 years, 1184 cases of peptic ulcer have been studied and followed in the Gastro-enterological Clinic of our division. Of these, approximately 10% (112 cases) have been surgically treated and the remainder carried under medical care. Reviewing age incidence and sex distribution of these cases, it was found that approximately 88% (1050) were males and only 12% (134) females. The incidence of duodenal ulcer was 89%; of gastric ulcer 11%. The average age was 35.

In view of the apparent sex-linked character of this disease, we decided to reexamine the known effects of hormones on the gastric and duodenal mucosa and to add to this the clinical and experi-

mental data we have gathered to date.* Although we have had a large experience with various hormones in the treatment of gastroenterologic conditions, we have only presented those in which the follow-up has been of sufficient time (1 to 5 years) to make the observations of value.

For several years medical literature has contained clinical and experimental reports on the effects of the isolated hormones and vitamins on the stomach and duodenum. In our attempt to collect and summarize the knowledge of hormonal effects on the gastroduodenal mucosa, we realize that there are many omissions due to the limitations inherent in an article restricted in size and scope.

Chemical synthesis and physiologic studies are rapidly disclosing the close relationship between vitamins and hormones. Several effects of vitamins A, B complex, C and D on the gastric mucosa and gastric musculature have been determined.

Vitamin A exerts a control on epithelial growths and proliferation,^{27,66} has been shown to affect the type of cell formation, and to cause extraordinary tissue proliferation in the gastric mucosa of experimental animals.¹⁸ Vitamin B complex deficiency causes marked delay in the emptying time of the stomach²³ and a lowering of gastric acidity.⁵²

Mucosal changes due to lack of vitamin C disturb gastric function⁵⁸ by what is thought to be an action on the blood supply of the mucosa. In traumatic injuries, which are probably frequent in the stomach, vitamin C deficiency causes a failure of the proliferating mesodermal cells to mature and collagen formation is impaired.⁴¹

Cod-liver oil depresses gastric mucosal activity and slows the motility of the stomach.⁵⁰ This inhibition of secretion and motility is not completely a local but a humoral effect and is probably due to the release of enterogastrone.²⁹

Endocrines are dependent on the conversion of vitamins for their synthesis and metabolism.³ It is probable that at least part of the influence on cellular tissue growth and glandular secretions attributed to vitamins is indirect, and due to hormone anabolism, metabolism and consequent activity.

Gastric hypersecretion in hyperthyroidism has been noted by several authors.^{11,56}

Various effects of thyroid administration on gastric secretion have been described by Katz,⁴⁴ Badykies,¹⁰ Lewit,⁵³ Hardt,³⁷ and Truesdell.⁶⁵ A recent careful and authoritative study shows that in hyperthyroidism there is an increased percentage of achlorhydria, increased prominence of gastric rugae, an earlier start to gastric emptying time, and a delay in complete emptying time.¹⁴

Removal of the parathyroids depresses gastric secretion⁶⁵ and

* Further studies were intended but we are publishing our findings to date, as one of us (R. H. A.) has been called to active duty in the Medical Corps of the U. S. Naval Reserve.

overdosage of parathormone abolishes gastric secretion due to extensive hemorrhage into the gastric mucosa.⁷ The relationship of the parathyroid to the gastric secretion has been established and summarized by Babkin and his associates.⁹ They report that repeated administration of parathormone affects first the nervous phase and then the chemical phase of gastric secretion; the volume, acidity and peptic activity all diminish proportionately to the degree of hypercalcemia.

Although the results show some variation, insulin increases the free acidity and depresses gastric motility.³² Over 80% of severe diabetics have hypochlorhydria.¹³

The means by which the mucosa of the pyloric end of the stomach affects the production of secretions from the cardia and fundus have not as yet been completely established, but there is sound experimental evidence to show that the hormone "gastrin"^{24,25,48} is produced and thrown into the blood stream by the pyloric mucosa, which instigates this process. Despite lack of confirmation by Finsterer³⁰ and Wangensteen,⁶⁷ the work of several investigators leaves little doubt concerning an endocrine action. Because of the similar action of histamine upon the gastric mucosa, several authors believed this hormone to be histamine; however, recent work on isolated and denervated gastric pouches with histamine-free extracts demonstrates the true hormonal character of the internal secretion of the gastric mucosa.^{8,12,34,35} The means by which the liberation of secretin, cholecystokinen and enterogastrone, all internal secretions of the duodenum, are accomplished are still not completely clear; probably it is partly due to the arrival of acid contents of the stomach, and sometimes influenced by hormonal control.¹⁷ Hormones from the intestine, secretin,⁴² cholecystokinen,⁴³ and enterogastrone³¹ also affect the gastric mucosa. It has been shown that the internal secretion of enterogastrone, which depresses gastric secretion,²⁰ activates and stimulates the duodenal mucosa. A substance recovered from urine, urogastrone, probably excreted enterogastrone, suppresses gastric secretions.³⁶

Adrenalectomy depresses gastric secretion. In Addison's disease the gastric secretion shows either hypo-acidity or an achylia.⁵⁹

Pituitrin depresses gastric secretion.⁵⁷ In acromegaly and Froehlich's syndrome, gastric secretion is often decreased.⁵⁴ Recent experiments and clinical findings show that the gonadotropic substances in the blood stream influence the activity of the gastric mucosa. The anterior pituitary-like fraction of pregnancy urine depresses gastric secretion.¹⁹ De Lisi²¹ believed that the depression of gastric secretions following the administration of anterior pituitary-like substance is secondary to its effect upon the thyroid and ovaries. One of the hormones from the pars posterior of the pituitary gland, vasopressin, affects the activity of the gastric mucosa, by

virtue of its control of the blood flow to the secretory glands. Injections of large doses of this substance will produce extensive hemorrhagic lesions into the acid-producing portion of the stomach, and inhibition of gastric secretions.²²

Increased acid secretion in dogs has been noted in transplanted gastric pouches during lactation.⁴⁷ Gastric hypersecretion has been noted following parturition.⁴⁰ Gastric acidity is reduced during pregnancy. Peptic ulceration rarely occurs during this period and if it was present prior to gestation, a remission usually takes place.^{4,64} This has been thought to be due to increased blood estrogen,⁶⁹ but further observations following estrogen injections in animals and humans have failed to verify this finding.^{5,62} Estrogens in males over 60 increase appetite, and oral and parenteral overdosage of estrogenic substance (stilbestrol) has produced nausea, vomiting and epigastric pain.^{15,26,49} We do not believe this to be completely a local irritative effect as has been thought by some, but a hormonal effect on the gastric mucosa.

Males and females have an approximately equal number of peptic ulcers before puberty, when their hormonal balance is as yet not well established; following puberty and synchronously with the change in the androgen estrogen ratio, the peptic ulcer ratio changes to 9 males per 1 female.^{46,60} The incidence of achlorhydria definitely increases with age. Peptic ulcer occurs frequently in females during and immediately following the menopause.

These evidences of endocrine control of the gastroduodenal mucosa have encouraged us to study the results of changing the hormone balance in males by the intramuscular injection of estrogens.

Method. Twenty-two men, all with protracted histories of chronic duodenal peptic ulcer, who had been previously under other treatment unsuccessfully in our Gastro-intestinal Clinic for at least 1 year (usually longer) were placed on daily (except Sunday) injections of various dosages of estrogenic substance (theelin in oil). All injections were given in the same clinic, by the same nurse in the same place (buttock). No further medication was given unless specifically indicated (see Table 1).

Laboratory studies on all patients showed negative serologic tests for syphilis, urinalyses showed no abnormality, and basal metabolic rates were within normal limits.

SUMMARY OF TABLE 1. All patients were males and had positive x-rays for duodenal ulcer. Average age 39.2 years. The average length of time between diagnosis and beginning treatment in this clinic was 2.9 years (several had refused operation).

Of the 22 cases, 21 were followed for 1 to 3 months; 14 for 6 months to 1 year; 13 for 1 to 3 years; and 11 for 3 to 5 years.

TABLE 1.—TWENTY-TWO CASES OF DUODENAL PEPTIC ULCER IN MALES TREATED WITH PARENTERAL ESTROGENIC SUBSTANCE (THEELIN)

No.	Age	Years prior treatment in clinic.	Total No. injections	Internat. theelin per injection	X-ray report just before treatment	1 to 3 mos. after treatment	6 mos. to 1 yr. after treatment	1 to 3 yrs. after treatment	3 to 5 yrs. after treatment	Further treatment
						Clinical results	X-ray report	Clinical results	X-ray report	
1	38	3	20	4,000	+	Asympt.	+	Good	+	
2	44	2	21	4,000	+	Recur.	+	Recur.	+	Medical
3	41	2	18	6,000	+	Asympt.	+	N.D.	N.D.	
4	32	5	30	4,000	+	Good	+	Good	+	10 more injections, 10,000 units theelin
5	46	3	21	6,000	+	Good	+	Recur.	+	Surgical
6	40	2	18	6,000	+	Asympt.	+	N.D.	N.D.	
7	29	6	20	6,000	+	Asympt.	+	Unimpr.	+	Medical
8	60	2	19	6,000	+	Asympt.	+	N.D.	N.D.	
9	39	1	30	6,000	+	Good	+	Good	+	10 more injections, 10,000 units theelin
10	46	3	21	10,000	+	Good	+	Good	+	None
11	34	2	20	6,000	+	Good	+	N.D.	N.D.	
12	34	4	18	6,000	+	Asympt.	+	N.D.	N.D.	
13	32	2	21	10,000	+	Asympt.	+	Operation—died	+	
14	47	3	21	10,000	+	Unimpr.	+	N.D.	N.D.	
15	33	1	18	10,000	+	Asympt.	+	Asympt.	+	Medical
16	49	2	21	10,000	+	Good	+	N.D.	N.D.	None
17	25	6	20	6,000	+	Asympt.	+	Asympt.	+	
18	50	7	18	6,000	+	Good	+	Oper.	+	Medical
19	43	3	21	10,000	+	Good	+	Good	+	Medical
20	35	2	24	10,000	+	Asympt.	+	Unimpr.	+	Medical
21	37	2	26	10,000	+	Asympt.	+	Recur.	+	Medical
22	29	1	18	10,000	+	N.D.	N.D.	N.D.	N.D.	

NOTE.—Upon recurrence of symptoms, oral medication was resumed. Asympt. = Asymptomatic. Good = Definitely improved with mild residual gastro-intestinal symptoms. No further medication required. Unimpr. = Unimproved. Medication causes no change in gastro-intestinal symptoms. Recur. = Recurrence of previous severe ulcer symptoms. N.D. = No data. Patients did not return for follow-up studies. Oper. = Operation.

CLINICAL RESULTS

X-RAY

22 cases followed for 1 to 3 months:

1 Recurrence of severe symptoms (worse)	7 Negative x-rays after treatment
1 Unimproved	14 Positive x-rays after treatment
8 Good results. Mild residual gastro-intestinal symptoms	
10 Asymptomatic following treatment	
1 Results unknown	

14 cases followed 6 months to 1 year:

5 Recurrences of severe symptoms	1 Negative
3 Unimproved	12 Positive
4 Good. Mild residual gastro-intestinal symptoms	1 Unknown
2 Asymptomatic	

13 cases followed 1 to 3 years:

7 Had recurrences	3 Negative
2 Unimproved	10 Positive
5 Good results. Mild residual gastro-intestinal symptoms	
1 Asymptomatic	
2 Operated upon (1 asymptomatic; 1 died)	

Two cases with former good results and recurrences had 10 further injections each of 1000 units of theelin, 10 and 12 months respectively after the original injections. These patients are reported as good (improved but with occasional gastro-intestinal upset) and unimproved, respectively, 1 to 3 years following treatment.

11 cases followed for 3 to 5 years:

8 Had recurrence	4 Negative x-rays (2 operated cases)
3 Good	7 Positive
3 Asymptomatic	
3 Unimproved	
1 Operated upon (asymptomatic)	

Seven patients were given gastric test meals both before and after treatment; the second test, however, was performed at varying intervals following treatment (1 week to 2 months). Although several were above normal limits prior to treatment, the free and total acid either remained above normal or was perceptibly higher following treatment. No cases showed a fall in either free or total acid, despite clinical and x-ray improvement.

The results of estrogen administration occurring in this group (Table 1) seemed worthy of further investigation; in addition, therefore, we followed 9 cases from 10 to 18 months (1940-41) with additional studies. Using larger doses of estrogenic hormone, urine estrogen studies, gastric analyses, and gastroscopic examinations were made.

GRAPH SHOWING INCREASE IN GASTRIC ACIDITY AFTER ESTROGEN ADMINISTRATION

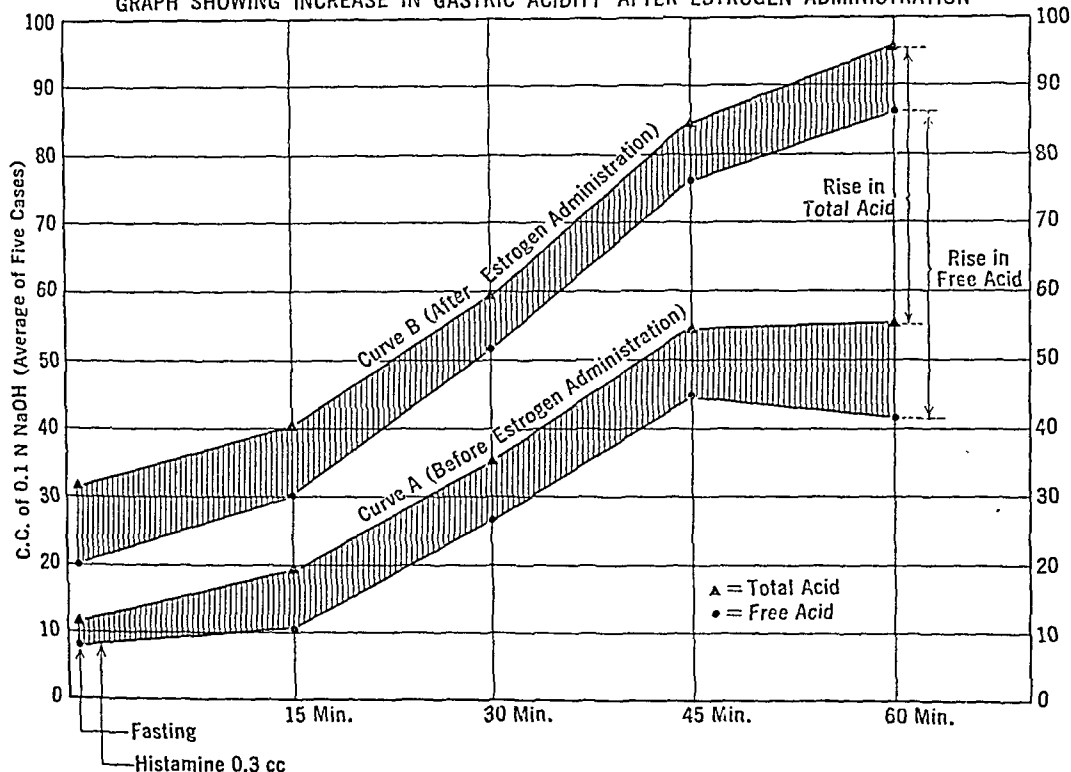


FIG. 1.—Increase in gastric acidity before and after estrogen injections. (Cases 1, 2, 3, 4 and 5 of Table 2).

Seven male patients with active symptoms caused by chronic duodenal peptic ulcer, who had been treated in our clinic for more than 1 year, were placed on large doses of theelin (estrogenic substance). From 200,000 to 700,000 international units of theelin were given by daily (except Sunday) intramuscular injection in 10 to 50,000 unit doses. During the period of injections no other medication was given except placebos when necessary.

Two of the males chosen had had theelin injections with remission and recurrences previously (1937—Case 4; 1938—Case 9—Table 1), and incidentally requested further injections.*

* Two female patients suffering from duodenal ulcers of 5 to 18 months' duration, and having menopausal symptoms, were also treated. In the females the theelin was given at longer intervals (1 to 2 times weekly). On these cases we have either insufficient laboratory work or follow-up to evaluate the results and they will therefore not be taken into consideration in the calculations and conclusions.

TABLE 2.—NINE CASES OF DUODENAL PEPTIC ULCER TREATED PARENTERALLY WITH ESTROGENIC SUBSTANCE.

Case No.	Age	Duration of clinical symptoms	X-ray report prior to injection of thecln.	Previous treatment	R.U. estrogen per 24 hr. urine per 1000 cc. urine	No. of injections	Inter- national units per injection	Clinical course during treatment and following treatment	X-rays following per 24 hr. urine per 1000 cc. urine	Clinical course at 6 mos. following treatment	X-rays at 1 yr. following treatment	9†
1	52	20 yrs.	Medical endocrin.	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	9†
2	47	10 yrs.	Medical endocrin.	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	47
3	41	2 yrs.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	41
4	36	2 yrs.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	36
5*	49	10 yrs.	Pylosus + Surgical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	49
6*	50	2 yrs.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	50
7*	44	11 yrs.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	44
8†	41	5 mos.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	41
9†	47	8 mos.	Medical	Medical	20	13	50	Good	15.8	Unimpr.	Asympt.	47

Asympt. = Asymptomatic.

X-ray realiti; + = Ulcer present.

X-rays at 6 mos. = 1 yr. fol-

Clinical course at 1 yr. fol-

X-rays at 1 yr.

Good = Feels well; occasional gastro-intestinal symptoms. No further medication.

X-ray realiti; + = Ulcer present.

X-rays at 6 mos. = 1 yr. fol-

Clinical course at 1 yr. fol-

X-rays at 1 yr.

N.D. = No data.

Recur. = Recurrence of severe

Hospitalized

Recur. 10 mos. Recur. 11 mos.

Unimpr. +

In this publication we are only considering males.

No sign of lesions. = No sign of lesions.

Case 7 showed electrocardiographic evidence of myocardial damage.

Case 7 showed electrocardiographic evidence of myocardial damage.

Case 7 showed electrocardiographic evidence of myocardial damage.

Studies of the 24 hour urine output for measurement of the amount of estrogenic hormone present were performed before and following theelin injections.

Blood and urine estrogen studies were made prior to and following treatment in 8 of the 9 cases tabulated in Table 2. All but 1 case showed a rise in urine estrogen following treatment. Neither urine nor blood androgens were investigated and therefore the status of the androgen-estrogen ratio is not known. The work will have to be repeated to ascertain these facts.

Five cases (Table 2) had gastroscopic examination previous to estrogen administration; unfortunately, however, only 2 cases were so examined after treatment. Although in these 2 cases (3 and 7 of Table 2) which were asymptomatic at the time of gastroscopy, despite a marked rise in gastric acidity, the gastric mucosa was apparently normal; there is no method of ascertaining the condition of the duodenal mucosa by direct vision. We cannot overemphasize the importance of gastroscopy in determining the physiologic and pathologic status of the gastric mucosa. Further evidence of gastroscopic changes in a larger series of cases is being prepared and will be published in a separate report.

SUMMARY OF TABLE 2. All cases treated showed clinical improvement during and immediately following treatment. Of the 7 males, 4 were asymptomatic and 3 felt generally well but had occasional mild gastro-intestinal symptoms—heartburn, belching, slight epigastric pain, etc.—which did not, however, require further medication. X-rays of the stomach and duodenum which had been previously positive were completely reversed to negative (—) in 2; 3 showed evidence of healed lesions (\pm) but no evidence of activity; and 2 remained positive (+).

At 4 to 6 months following treatment 2 cases remained asymptomatic; 2 felt generally well but had occasional gastro-intestinal disturbances. Two cases were unimproved and needed further medication due to gastro-intestinal complaints. One case had recurrence of severe acute symptoms starting 5 months after injections.

Gastro-intestinal x-ray checkup at this time on 5 of the 7 patients showed 1 case with signs of a healed lesion but without activity, and showed the remaining 4 positive for duodenal ulcer.

Further follow-up showed 5 cases had recurrences of acute symptoms, at 5, 10, 11, 11 and 13 months respectively, and 3 required hospitalization. One case failed to return. A single case showed signs of a healed duodenal lesion and the remaining 6 cases showed positive x-ray evidence of duodenal ulcer.

Gastric test meals (with histamine stimulation) were performed 1 day to 1 week prior to theelin injection and within 1 week following the last injection. The method of gastric analysis employed was as follows:

The patient came in without breakfast. A Levine tube No. 18

was passed through the nose into the stomach, and a fasting specimen of about 30 cc. collected and labeled as such. Then $\frac{1}{3}$ cc. of histamine was given by subcutaneous injection. A test meal specimen of about 10 cc. was then taken and labeled No. 1, and after that at 15 minute intervals additional specimens to a total of 4 were collected and labeled, No. 2, No. 3 and No. 4 respectively.

TABLE 3.—RESULTS OF GASTRIC TEST MEALS

	Before		Following		Total increase	
	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid
1. Fasting . . .	0	2	15	21		
1	0	6	20 5	32		
2	34	42	42	49		
3	60.5	66	71.5	84		
4	64	74	88	110		
	158.5	190	237.0	296	78.5	106.0
2. Fasting . . .	10	14	14	15		
1	12	23	22 5	24		
2	36	46	36	40		
3	56	74	70 5	74		
4	70	83	96	100		
	184	240	239 0	253	55 0	13 0
3. Fasting . . .	0	2	0	9		
1	0	4	5 5	15.5		
2	0	4	30	43		
3	20	26	60	68		
4	10 5	30	79	86 5		
	30 5	66	174.5	222.0		
4. Fasting . . .	15	15	50	72	144.0	156.0
1	25	39	73	81		
2	37	55	91	98		
3	54	72	106 5	111		
4	65	78	87	93		
	196	259	407 5	455	211 5	196 0
5. Fasting . . .	15	23	22	37		
1	16	23	30	47		
2	25	29	59	67		
3	33	36	71	84		
4	0	12 5	80	89		
	89	123 5	262	324	173 0	200 5

Three cases (2, 3 and 4) showed a moderate degree of hyperacidity and 2 cases (1 and 5) showed normal gastric acidity prior to estrogen injections. All showed a tremendous increase in free and total acidity following the injections of estrogens: increase of 40% to 180% free acid; of 22% to 164% total acid. It is possible that the increase would have been more marked in Cases 1, 2, 3 and 5 if further specimens had been taken.

A word concerning the interpretation of x-ray results. There is no difficulty with definitely negative or distinctly positive plates.

However, a problem arises in the interpretation of those which have been reported as "evidence of previous inflammatory disease," "slight residual deformity," "minimal deformity, findings suggest healed ulcer," "no sign of activity at present," which we have listed as \pm in Table 2. We both respect and appreciate the integrity of the roentgenologists of this institution in their efforts to help us diagnose these rapidly changing lesions. We believe it is particularly difficult to determine whether these duodenal lesions which we have grouped as \pm are due to scarred healing or early re-occurrences at the original site.

It is not surprising that the injection of estrogens in males showed an increase in gastric mucosal activity. It has been shown that the anterior pituitary-like gonadotropic substance will lessen the amount of gastric secretion and lower the free and total acidity.^{19,21,60} In several other instances anterior pituitary gonadotropic substance and estrogens act in an opposing manner. We^{16,28,33,63} are in agreement with others^{5,61} that estrogens do not depress the quantity and acidity of gastric secretion. There seems to be a discrepancy in the relationship between the healing of duodenal peptic ulcers and the gastric acidity. With the increase of blood estrogen levels they appear to heal in the presence of an increased gastric acidity. Winkelstein, having treated 20 women showing menopausal symptoms combined with "ulcer symptoms" with 20,000 units of Progynon B injected 3 times weekly, states that there was no notable change in the acidity curves. Although x-rays were taken, the results are not given; though there is no definite follow-up, "clinical improvement persisted for some months." Recurrences were frequent but usually relieved by further injections. He concludes that in this group, estrogen therapy was instituted with good results and believes it an open question as to whether the improvement was due to a specific effect on the gastric mucosa or the relief of the neurovascular symptoms of the menopause.⁶⁸ Assuming an alteration in the androgen estrogen ratio caused by parenteral estrogen injections, it seems logical to assume that results in males will differ from those in females.

The problem of evaluating therapeutic results in any group of peptic ulcer cases is fraught with difficulty; we would be extremely gullible to come to definite conclusions, ignoring the many factors involved in the life cycle of a lesion as evasive and poorly understood as peptic ulceration. In the realization that spontaneous remissions are characteristic of this condition, we feel that a consideration of the nutritional, psychoneurogenic, and (we shall add) endocrine factors is paramount in an attempt to come to an understanding of the phenomena which take place. We have, however, several groups of patients who act as controls, to which these results could be compared, *i. e.*, those who were receiving various other oral and parenteral drugs during the same period. The great importance

of a long and careful follow-up is clearly shown. It is self-evident from the tables that if the cases had not been studied continuously and over a protracted period the results would be misleading.

In the larger, longer followed group (Table 1), the 1 to 3 month checkup of 21 of 22 cases showed 10 (47.6%) asymptomatic, and 8 (37.1%) improved enough not to require further medication. This 84.7% (47.6 plus 37.1%) shows definitely more improved cases than we see with control groups (the latter varies from approximately 38% to 70%. In 7 cases (33.3%) the *x*-rays, previously positive, had become completely negative in a short period. The best results in the control groups during the same time period show approximately 20% reversal of *x*-ray evidence.

At the 6 months to 1 year period, of 14 out of 21 cases, only 2 had remained asymptomatic, but 4 were definitely improved. Only 1 *x*-ray remained negative. Five cases had recurrences of symptoms. At the 3 to 5 year follow-up, 3 cases were asymptomatic, 3 greatly improved, and 4 had negative *x*-rays. However, of those who were asymptomatic (with negative *x*-rays), 2 had already been subjected to subtotal gastrectomy. These results, as far as the percentage of those who come to surgery is concerned, are comparable with the results of all other treatments at our clinic, *i. e.*, approximately 10% come to surgery (all receive subtotal gastrectomy).³⁸ All that can be said for the therapeutic results in this group (Table 1) is that daily parenteral injection seemed to have caused a larger percentage (84% against 48% to 70%) of remissions and reversal of *x*-ray evidence (33.3% against 20%) in the course of the duodenal peptic ulcer. These remissions and reversal of *x*-ray positivity were definitely transitory in character, reverting to the average of the controls in 3 to 6 months to 1 year following treatment.

In the second group (Table 2), considering the 7 male patients only at the 3 month follow-up, 4 were asymptomatic and 3 definitely improved. Two had complete reversal of a previously positive *x*-ray and 3 showed residual scarring in the duodenum but no evidence of activity. However, 6 months later only 2 remained asymptomatic; 2 were definitely improved, and 1 case had recurrence of symptoms at 5 months. Of the 5 *x*-rayed, 1 showed residual scarring and 4 were positive for duodenal ulcer. At 1 year (only 6 cases followed), 1 case (whose *x*-ray showed evidence of a healed ulceration but no activity) remained asymptomatic and the remaining 5 cases had recurrence of severe symptoms at 5, 10, 11, 11 and 13 months respectively, with positive *x*-ray findings.

These results would tend to verify our conclusions concerning cases in the previous series (Table 1) that daily parenteral estrogen injection in the dosage given, causes a higher percentage of remission in chronic duodenal ulcer, lasting from 5 to 10 months, than found in controls. The transitory nature of this remission (in Table 2) is particularly marked. Although the number of cases in this group is too small to sample for mathematical calculation, the results seem

clear-cut. Of greater importance than the subsidence of symptoms (in the clinical course of peptic ulceration) is the healing of the duodenal lesion. This change in the lesion (Table 2) occurred in 5 cases (as evidenced by *x*-ray) in the presence of a markedly increased free and total acidity (Table 3). It seems to cast doubt on present views concerning the relationship between the healing of a duodenal ulcer and lowering the gastric acidity. Others who have experimented on an entirely different basis have come to similar conclusions (at least as far as antacid therapy is concerned).⁵¹ It is not possible with our present knowledge to determine whether the healing of the peptic ulcer was due to a direct effect of estrogens on the duodenal mucosa or whether the healing is secondary to the effect upon the gastric mucosa and its secretions.¹⁷ Further animal experimentation will be necessary to determine this point.

In the second group (Table 2) we paid especial attention to endocrinopathies resulting from the large doses of estrogens given. Three patients developed gynecomastia; 2 developed loss of libido. These manifestations lasted from 2 weeks to 2 months following treatment and then completely disappeared.

Prostatic examination on all patients showed no evidence of abnormality.

Experiences of several observers^{6,55} have emphasized the inherent dangers in continual hormone injection, especially in large doses. We are in no way recommending hormone therapy as routine treatment in peptic ulcer and would add our warning to that of others on the possible carcinogenic activity of these powerful agents. It is possible that in a patient with a threatening perforation, on whom operation was not feasible, hormone therapy would be applicable.

In previous publications^{2,39} we have called attention to the relationship between the androgen estrogen ratio and the gastric mucosa in carcinoma of the stomach. We believe that the clinical and experimental work reported above furthers this concept. Loeb⁵⁵ has stated that the sex hormones influence the inception of malignancy in those tissues which they affect; the gastric mucosa is affected by the change in the androgen estrogen ratio brought about by the administration of estrogens. Further studies on this subject are at present being completed for future publication.

Summary. 1. Clinical and experimental evidence of the endocrine character of the secretions of the gastroduodenal mucosa is reviewed.

2. Attention is called to the sex linked factors in peptic ulceration.

3. The favorable, though largely temporary, results of parenteral administration of estrogen (theelin) on the gastroduodenal mucosa of 29 male patients with chronic duodenal peptic ulcer are noted.

4. The possible relationship between the androgen estrogen ratio and gastric carcinoma is pointed out.

Acknowledgment is made of the assistance provided by Parke, Davis & Co. in furnishing a grant to cover part of the expenses in carrying out this study.

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THE TWO-DOSE GLUCOSE TOLERANCE TEST*

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PART 1

SUGAR tolerance tests have been used for many years and have a definite place in the evaluation of carbohydrate metabolism. The chief objections to the usual type of sugar tolerance test include the need for 5 needle punctures and 5 determinations of sugar in the blood and urine, the 3-hour period required, and the insufficiency of information with regard to the ability of the patient to metabolize glucose. As a consequence, many physicians who desire more information about their diabetic patients than is disclosed by urinary tests secure a single blood specimen. Usually this is a specimen of blood obtained in the morning when the patient has fasted overnight.

In 1931 Exton and Rose³ devised a sugar tolerance test which required only 3 specimens of blood. Their procedure was as fol-

* Supported by a grant from an anonymous donor and by the Rockefeller Fluid Research Fund.

lows: 2 packages each containing 50 gm. of glucose were made up and each dissolved in 200 cc. of water to which orange or lemon juice was added to flavor. Fifty gm. of glucose were given and the blood and urine were collected. Thirty minutes later another 50 gm. of glucose were given and blood and urine were again collected. Thirty minutes later blood and urine were collected for the third time. The criteria of a normal response were that the final blood sample should be less than or only slightly higher than the peak, and that the total urinary excretion should be less than 100 mg. Renal glycosuria was indicated by a low flat blood sugar curve with higher excretion; alimentary glycosuria by sharp distinct peaks with low or only slightly higher final values and urinary excretion of over 100 mg. Diabetes was diagnosed if the final specimen was 10 or more mg. higher than the peak and excretion was over 100 mg.

This test was based on the paradoxical law of Allen,¹ who found that there was no limit of tolerance to glucose given by mouth to the normal animal. On the other hand, in diabetic animals there were real definite limits of tolerance. Rabinowitch² applied Allen's law to differentiate the glycosurias of diabetes and hyperthyroidism. He gave diets of constant protein and fat composition and increased the amount of carbohydrate daily by the administration of added glucose in small amounts at frequent intervals. The Exton-Rose test utilizes these results and the Hamman-Hirschman phenomenon,⁴ which is, that after successive doses of dextrose given by mouth, the level of each successive rise in the blood sugar curve is lower than the preceding one. The first peak is reached in about $\frac{1}{2}$ hour, with a discrepancy in normals and diabetics; this discrepancy is greatly accentuated at 1 hour. Matthews, Magath, and Berkson⁵ suggested that the Exton-Rose test might be simplified by the omission of the fasting and the $\frac{1}{2}$ -hour samples of blood sugar. Such simplification would be highly desirable if the power of the test to diagnose and assess the progress of diabetes at a given time were not sacrificed. With a view toward determining the best single end point for a one-puncture tolerance test, the Exton-Rose procedure is here modified to compare 4 definite end points.

Methods. The procedure was as follows: The patient took no food or insulin after his evening meal. Water was allowed as desired. He appeared at the clinic at 8.30 to 9 A.M., having eaten nothing and drunk nothing except water or black coffee. He lay down on a couch quietly for 15 to 30 minutes before the test was begun. The fasting blood sugar and urine were then taken. He was given 325 cc. of water containing exactly 50 gm. of glucose flavored with 2 to 3 tablespoonfuls of lemon juice.* Thirty minutes after the glucose the blood and urine were again taken and another 50 gm. of glucose were given as above. Thirty minutes after the second glucose the third, and after another 60 minutes the fourth, samples of blood

* This is approximately a 15% solution, in which concentration glucose is ordinarily absorbed from the gastro-intestinal tract.

and urine were taken. Qualitative and quantitative tests were done on the urine. All blood sugars were done by one technician with a few exceptions.* This procedure differs from that of Matthews, Magath and Berkson⁶ only in that a fourth specimen of blood and of urine are examined.

Classification of Material. The present series is composed of 110 glucose tolerance tests done on 105 individuals. All except 7 were on patients who were being followed in the outpatient endocrine clinic of the Stanford University Hospitals. All came from their homes to the clinic for the test. There were 32 non-diabetic individuals, 16 of whom were overweight by 30% or more, and 16 of whom were less than 30% overweight. There were also 3 cases of renal glycosuria. The remainder of the patients had diabetes. The diabetes was classified as mild, moderate, severe, or extreme by one of the clinicians in the diabetic clinic (Drs. Cutting, Gray, or Robson). Mild diabetes was said to be present clinically if the patient remained free from glycosuria on a diet containing more than 140 gm. of carbohydrate; moderately severe diabetes was diagnosed when insulin was needed with such a diet; severe diabetes was considered present when more than 40 units of insulin was required in order that the patient on such a diet remain free from glycosuria. It may be stated that the clinical criteria were not rigid and depended a good deal on the judgment of the clinician making the evaluation. Such evaluations were generally made before the test was performed and in all cases were made without knowledge of the results. It is to be noted that this series was heavily weighted with individuals who were considered to be normal except for the presence of obesity. It has been part of our objective to determine the significance of the test in such individuals. A number of tests have been done on individuals with other diseases but were not included in the analysis of this series with the exception of 2 cases of hemachromatosis with severe diabetes.

Blood Sugar Curves for Each Class. An arbitrary classification based on the 1-hour blood sugar level was established as follows:

Sugar	Classification
Less than 158	Non-diabetics
158-179	Doubtful diabetes
180-260	Mild diabetes
Over 260	Moderate to severe diabetes

These criteria are modified from those of Matthews, Magath and Berkson,⁸ who found that 95% of their patients with blood sugar levels less than 158 mg. per 100 cc. were designated in agreement with the clinical findings and that all of the patients with diabetes had 1-hour blood sugar values over 158 mg.

From this classification Table 1 was derived. These data are presented graphically in Figure 1. Observation of this chart and

* We are indebted to Mrs. Virginia B. Pomeroy for the blood sugar determinations and to Mrs. Margaret Curtis and Mrs. Betty Saxe for valuable assistance in the Clinic.

of Table 1 indicates a steady rise in the average values for all points on the time curve as the degree of diabetes increases. The fasting values, however, do not differentiate among normal persons, persons with renal glycosuria and borderline diabetics; nor do the $\frac{1}{2}$ -hour specimens, although the range in the latter group is wider than in the former. In the specimens taken at 1 hour, or $\frac{1}{2}$ hour after the second dose of glucose, the differentiation among these various groups is clear-cut; in these specimens there is also a difference between the so-called normal individuals who are over 30% overweight and those who are less than 30% overweight.

TABLE 1.—AVERAGE BLOOD SUGARS IN MG. PER 100 CC. FOR EACH CLASSIFICATION OF DIABETES

Class	No. of subjects	Fasting			$\frac{1}{2}$ hour			1 hour			2 hours		
		M.*	SE.†	SD.‡	M.	SE.	SD.	M.	SE.	SD.	M.	SE.	SD.
Borderline to mild diabetes	6	105	3	8	160	6	15	193	9	23	143	12	29
Mild diabetes	34	118	4	26	189	7	40	215	6	37	177	9	50
Moderate diabetes . . .	17	136	9	38	225	12	51	296	10	42	274	21	86
Severe diabetes	16	192	10	38	286	8	32	378	9	36	414	13	52
Extreme diabetes (with hemochromatosis) . . .	2	262	45	64	345	55	78	430	46	64	483	57	81
All diabetes	75	141	5	47	220	7	61	273	9	81	255	14	118

* Mean.

† Standard error of the mean.

‡ Standard deviation.

The values of the specimens taken at 2 hours correspond in general with those taken at 1 hour. Among the normal patients and those with mild diabetes the 2-hour values show a lesser degree of accuracy than the 1-hour figures, with more overlapping of the normal and abnormal range. The 2-hour specimen, however, serves to distinguish more accurately between the more severe grades of carbohydrate metabolism.

Comparison with Results at the Mayo Clinic. Work on the present report was begun after reading the paper of Matthews, Magath and Berkson.⁸ The criteria offered by them for the evaluation of the 2-dose test seemed sound to us. We have compared our results with theirs as best we could, with the differences in clinical criteria in effect at the Mayo Clinic and at Stanford Medical School. Table 2 offers the best fit we can make between the two sets of clinical criteria.

Figure 1 shows a comparison between our data and theirs. It may be seen that there is a general parallelism between the two sets of curves in the diabetic patient material, which is closest in the 1-hour specimen. The borderline cases have almost identical curves. The remainder of the chart suggests that the groups designated mild, moderate, severe, and extreme with hemochromatosis by us are less severe than Grades I, II, III, and IV respectively of the Mayo series, with the difference between them varying from 8 to 16%. As explanation for the lower position of our 4 remaining curves it seems likely that our patients, being ambulatory, were

throughout somewhat milder; furthermore, we picked a larger proportion of patients with supposedly mild diabetes in order to evaluate the diagnostic merit of the test. Finally, the diets actually taken by our patients contained more calories and carbohydrate than we prescribed, whereas their diets being prescribed in the hospital were in fact eaten as ordered.

TABLE 2.—COMPARISON OF CLASSIFICATIONS USED IN THE MAYO CLINIC AND IN THE STANFORD DIABETIC CLINIC

<i>Mayo</i>	<i>Stanford</i>
Normal	Normal
Renal glycosuria	Renal glycosuria
Latent diabetes (Diagnosed by sugar tolerance tests only)	Borderline diabetes
Grade I ("Sugar-free on qualitatively restricted diet")	Mild (Sugar-free on diet containing 140 gm. CHO or more)
Grade II (Not more than 200 gm. CHO)	Moderate (Same with 30 U insulin or less)
Grade III (Same plus 30 U insulin or less)	Severe (Same with over 30 U insulin)
Grade IV (Same plus 30 U insulin or more)	Extreme with hemochromatosis

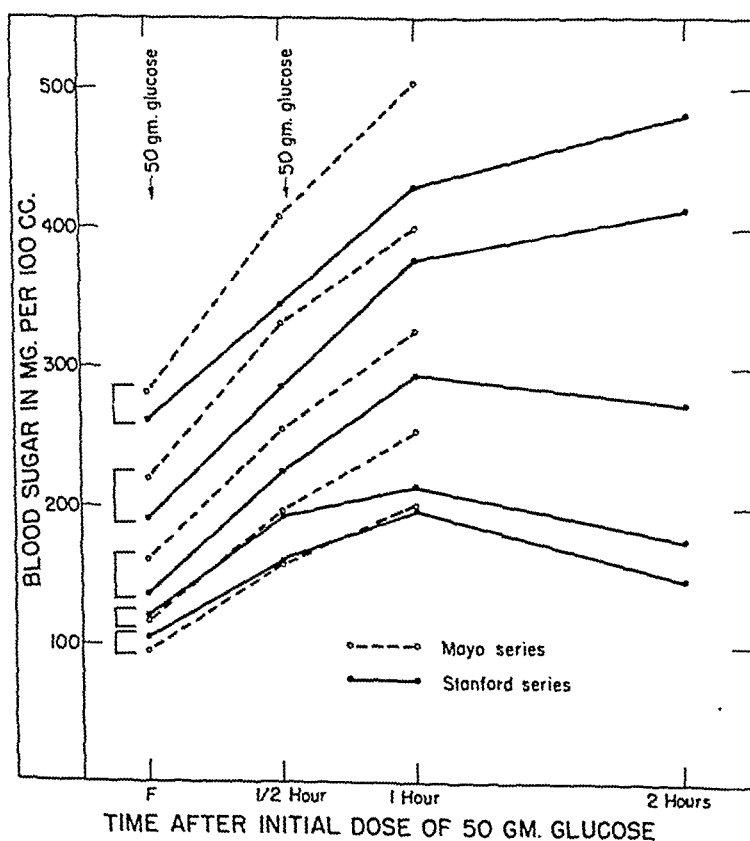


FIG. 1.—Average blood sugar curves of Stanford Series compared with Mayo Clinic.

Obesity. An attempt has been made to ascertain the effect of obesity on the 2-dose sugar tolerance curve. In the clinical classi-

fication the obese patients were included among the normal cases. Those with obvious impairment of carbohydrate metabolism were placed among the diabetic patients in the arbitrary method of classification according to the blood sugar level described above; the greater number of persons so affected were among those more than 30% overweight. The results demonstrated in Table 3 indicate that obesity definitely impairs the ability of the individual to endure the strain of the double load imposed by the 2-dose test. This is statistically significant only in the 1-hour value. We have not attempted to correlate statistically this impairment of tolerance with the duration of the obesity but it is our impression that our results would be similar to those of Short,¹⁰ who did find this a significant factor.

TABLE 3.—AVERAGE BLOOD SUGARS ON NON-DIABETIC PATIENTS

Class	No. of subjects	Fasting			½ hour			1 hour			2 hours		
		M.*	SE.†	SD.‡	M.	SE.	SD.	M.	SE.	SD.	M.	SE.	SD.
Renal glycosuria	3	87	9	16	147	9	17	129	12	21	98	10	18
Normal and obese up to 29% overweight	16	93	2	8	144	6	23	126	5	20	110	3	13
Normal and obese 30% or worse	16	95	2	8	149	4	16	140	6	24	119	5	18
All non-diabetics	35	93	2	9	146	3	19	132	4	23	113	3	17

* Mean.

† Standard error of the mean.

‡ Standard deviation.

TABLE 4.—AVERAGE BLOOD SUGARS IF CLASSIFICATIONS BE MADE PURELY BY GLYCOSURIA

	Fasting	½ hour	1 hour	2 hours
1. Non-diabetics	94	146	133	114
2. Borderline without glycosuria	105	163	190	141
3. Borderline with 0.25% glucose in urine or less. Diabetes without glycosuria during test	126	201	235	228
4. 0.1 to 5 gm.	120	195	235	199
5. Over 5 to 10 gm.	161	243	335	334
6. Over 10 to 15 gm.	199	290	366	368
7. Over 15 gm.	222	323	394	444

Glycosuria. An attempt was made to classify this aggregate of individuals according to the amount of glucose excreted during the course of the test. The results of this analysis, which are shown in Table 4 and Figure 2, demonstrate a remarkably close relation between the blood sugar values and the amount of glycosuria. The cases were fitted into 7 groups which are shown in the chart. There is a steady rise in the values for all points on the blood sugar curve, while the best fit with any single point on the curve is with the values of the 1-hour specimen. Blood sugar specimens are necessary to differentiate among the normal individuals, those with borderline diabetes and those with a high renal threshold. Among those who have glycosuria it may be said that a mild diabetic has 0.1 to 5 gm. sugar in the urine, a diabetic of moderate degree 5 to 10 gm. and a severe diabetic over 10 gm. The apparent discrepancy between Groups 3 and 4 is explained by the inclusion in the classi-

fication of "borderline diabetics" of certain obese individuals who never had had glycosuria but whose behavior during the test indicated their inability to metabolize carbohydrate.

The Best Single Determination. Among the 4 specimens taken in this series, the fasting blood sugar is of relatively little use in diagnosis. Many of the mild and some of the more severe diabetics are within the normal range. There is a gradual increase in values as the diabetes becomes more severe but the average values for the mild diabetics are still within the normal range. The $\frac{1}{2}$ -hour specimen shows a gradual rise in the averages from the normal to the

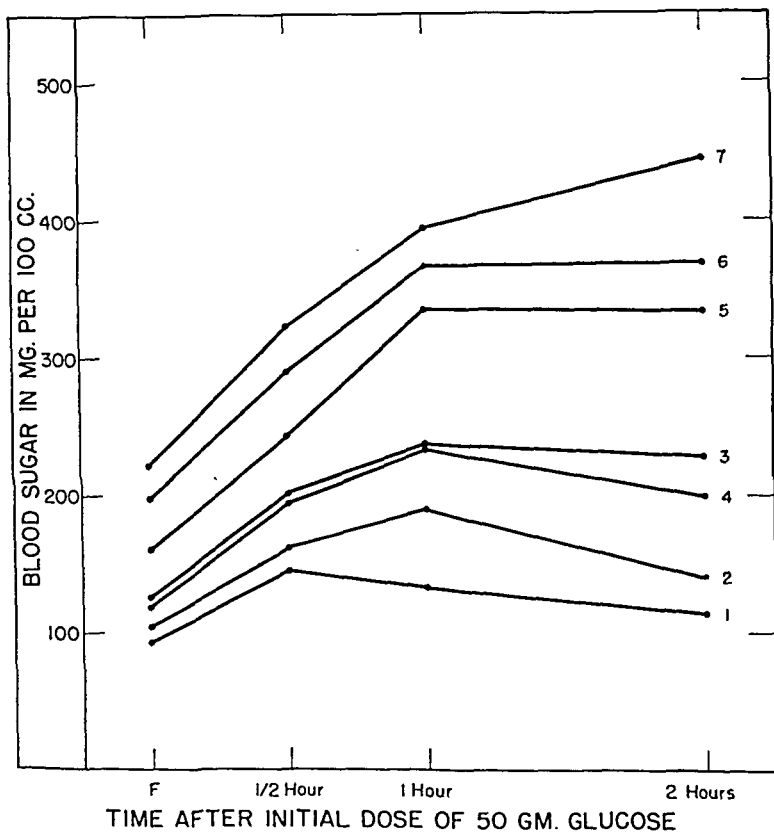


FIG. 2.—Average blood sugar curves obtained when classification is made solely on basis of glycosuria.

severe diabetic but the range is not at all distinct and the overlap is extremely wide. It is too dependent upon such factors as dislike for the test dose, poor gastro-intestinal motility, poor or delayed absorption, and previous diet.

The 1-hour values show a much better range and better correspondence in the determination of diabetes. We agree with Matthews *et al.* that the criteria used by Exton and Rose⁴ and those of Gould, Altshuler and Mellen⁵ are less accurate than the use of the single hour value as an indication of the presence of normal or abnormal sugar tolerance. In addition, these criteria are distinctly

more cumbersome and thus offer other difficulties to the widespread use of the test as a replacement for the single dose type. There is a steady increase in the values of the 1-hour determination as the diabetes grows more severe and the overlapping of the figures is not nearly so marked. As the diabetes becomes worse, however, there is much more of a jump. On the basis of these figures alone, one cannot distinguish so well the grade of severity of the diabetes.

For this purpose the 2-hour specimen seems to have a very definite value. It may be noticed that the average curves show an increasingly steep climb from fasting to 1 hour in the normal and in the mild diabetic. In the moderate to severe diabetic this steep curve continues to rise steeply whereas in the milder ones it tends to return to the lower levels. The 2-hour specimen is less valuable than the 1-hour in the diagnosis between normal and mild diabetic, but more so in the differentiation of the severity of the diabetes. The entire curve obviously gives the most complete evaluation of the ability to metabolize carbohydrate and is worth the trouble of the additional specimen. If economy is an object, as is so often the case in practice, the present paper warrants eliminating the fasting and $\frac{1}{2}$ -hour specimens since the 1- and 2-hour samples tell most of the story.

Comment. The behavior of the blood sugar after split doses of glucose is probably the best single criterion of the presence or severity of diabetes in an individual. However, in our series there were several individuals who had no history of diabetes, no glycosuria or other symptoms or signs, but who had a type of curve which was suggestively or definitely diabetic. Some of these individuals have had and others have not had any symptoms to date. There were also diabetic individuals who had an apparently mild diabetes, who had shown no glycosuria and no symptoms over a period of months or years on a moderately restricted, or in 2 cases on an unrestricted diet, whose glucose tolerance curves rose to extremely high levels at 1 and at 2 hours and who had moderate to very marked glycosuria.

This apparent discrepancy between the clinical evaluation of the state of the diabetes and the results of the test suggests that there is a difference between the adequate control of the diabetic and the ability of the pancreas to furnish sufficient insulin in a given period of time, or of the liver to utilize sufficient glucose in the synthesis of glycogen. To our way of thinking this does not detract from the value of the test.

Summary (Part 1). 1. The carbohydrate metabolism of non-diabetic and diabetic individuals has been examined by means of the 2-dose glucose tolerance test.

2. A classification of these individuals has been drawn up.

3. Tables and curves are shown for the averages in each group of cases.

4. The results of this series show a reasonable parallelism to those obtained by Matthews, Magath and Berkson.

5. Obesity impairs the ability of the individual to endure the strain of the double load imposed by the 2-dose test.

6. There is a close relation between the values of the blood sugar and the amount of glycosuria.

7. The 1-hour blood sugar value is the best single determination in the diagnosis of the existence of diabetes.

8. The 2-hour blood sugar value offers a means of differentiating the severer classes of diabetics.

PART 2

During the course of the study on the 2-dose glucose tolerance test it became apparent that it would be necessary to study the effect of varying diets. The procedure followed was the same as that outlined in the preceding Part 1. Five individuals were selected for this study. One was a nurse in the hospital whose diet was accurately determined by the hospital dietitian; a second was a clerk working in the diabetic clinic but eating at home; and the remaining were intelligent and reliable patients whose statements about the content of their diets were as accurate as is possible in a hospital out-patient department. All diets were outlined by us and worked out in detail by Miss Louise Esch, head of the dietetics division of the Stanford University Hospitals. Each diet was followed for a period of 2 weeks before the differentiating sugar tolerance tests were performed. The diets were rechecked at this time. In general, then, the tests represent successive 2-week periods.

TABLE 5.—TEST DIETS AND CURVES ON CASE 1; ARRANGED IN ORDER OF INCREASING CARBOHYDRATE CONTENT; IN CURVES 2 AND 3 IT WAS ESSENTIALLY IDENTICAL, WHILE THE FAT CONTENT WAS INCREASED

Diet	CHO	Prot.	Fat	Cal.	Fast.	$\frac{1}{2}$ hr.	1 hr.	2 hr.
1 . . .	55	72	206	2360	99	118	155	139
2 . . .	269	88	129	2589	93	123	133	119
3 . . .	248	87	220	3320	85	111	112	97
4 . . .	499	80	29	2577	82	84	56	75

Case Studies and Results. CASE 1. "Naturally thin" normal, a 26-year-old single nurse who had been underweight all her life in spite of repeated efforts to gain. Her weight varied from 99 to 103 pounds. She had no other complaints. She was placed on 4 different diets, each differing from the others in at least one respect, as is shown in Figure 3 and in Table 5, together with the results of the glucose tolerance tests made at the end of the fortnight on each of these various dietary régimes.

The results in this one case seemed sufficiently clear-cut, although they would have been even more orderly if the positions of the two middle curves were transposed: As the dietary carbohydrate was increased the sugar tolerance curve became flatter; the results of the two middle curves suggested that the absolute amount of dietary fat did not influence the tolerance.

CASE 2. Moderate obesity; a 28-year-old housewife whose chief complaint was an alleged gain of 27 pounds in 3 months, to 166 pounds. The basal metabolic rate was -16% . During consecutive 2-week periods she was placed on 5 consecutive diets which are shown in Figure 4 and Table 6, together with the results of the glucose tolerance tests made at the end of each of these dietary régimes. The weight varied a total of only 4 pounds.

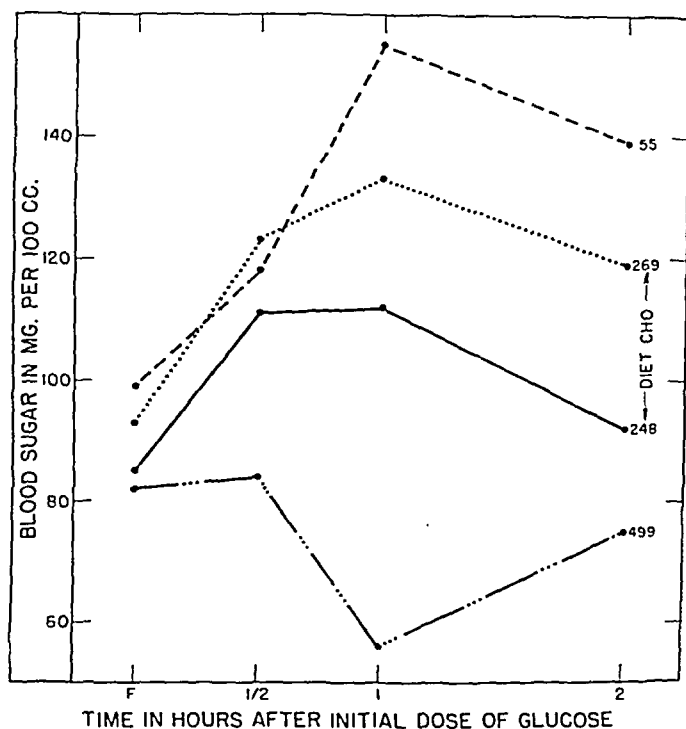


FIG. 3.—Blood sugar curves on Case 1.

In terms of the 2-dose test let us examine the levels at 1 hour, which is the level of greatest diagnostic import: The two worst curves were those in which the carbohydrate intake was 153 and 156 gm. The other 3 diets yielded results which were practically identical although the carbohydrate intake varied from 21 to 302 gm. Since the results were so thoroughly mixed, the necessary conclusion is that in some individuals, at least, the preceding diet does not have as much influence on the sugar tolerance curve as other factors in the individual, as yet unknown.

Incidentally, if one examines only the $\frac{1}{2}$ -hour specimen, it may be seen that the blood sugar became lower as the carbohydrate content was increased. This has been previously shown to be true for the conventional 1-dose glucose tolerance test.^{7,11} This inference as to the lack of dependency of the 2-dose test on the diet is distinctly different from the customary views with regard to

1-dose tests and therefore may appear paradoxical and confusing. On the contrary, the inference supports the hypothesis of superiority for the 2-dose test, since it can be used and interpreted when the prior diet is unknown, as is often the case, thus escaping a severe limitation of the single dose test.

TABLE 6.—TEST DIETS AND CURVES ON CASE 2; ARRANGED IN ORDER OF INCREASING CARBOHYDRATE CONTENT

Diet	CHO	Prot.	Fat	Cal.	Fast.	$\frac{1}{2}$ hr.	1 hr.	2 hr.
1 . . .	21	58	72	962	96	131	91	100
2 . . .	21	62	143	1619	94	139	89	103
3 . . .	153	66	9	957	100	130	111	104
4 . . .	156	75	78	1026	88	130	107	88
5 . . .	302	79	10	1614	93	125	89	83

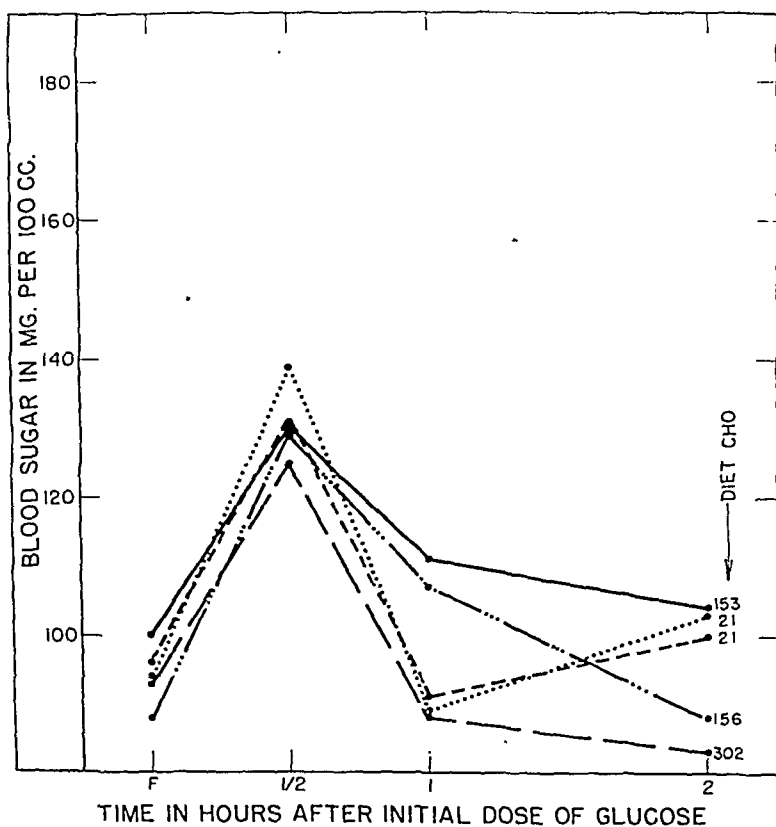


FIG. 4.—Blood sugar curves on Case 2.

CASE 3. Borderline diabetes; a 58-year-old barber who also had received 2 years' treatment for syphilis and had arteriosclerotic heart disease with auricular fibrillation. Glycosuria was discovered in April, 1939, and had been found off and on in the ensuing year. The weight varied from 164 to 177 pounds. He was put on the same set of diets as shown for the preceding patient in Table 6; the resulting curves are shown in Figure 5 and Table 7. Like the last case the results are without significant order and force the same inference, namely, that within fairly wide variations in carbohydrate and fat intake the results of the two-dose test are interpretable without the necessity of considering the prior diet.

TABLE 7.—BLOOD SUGAR CURVES ON CASE 3; THE DIETS WERE THE SAME AS THOSE IN CASE 2

Diet	Fast.	½ hr.	1 hr.	2 hr.
1	95	140	157	121
2	92	100	160	125
3	104	132	183	134
4	96	146	164	127
5	87	148	169	146

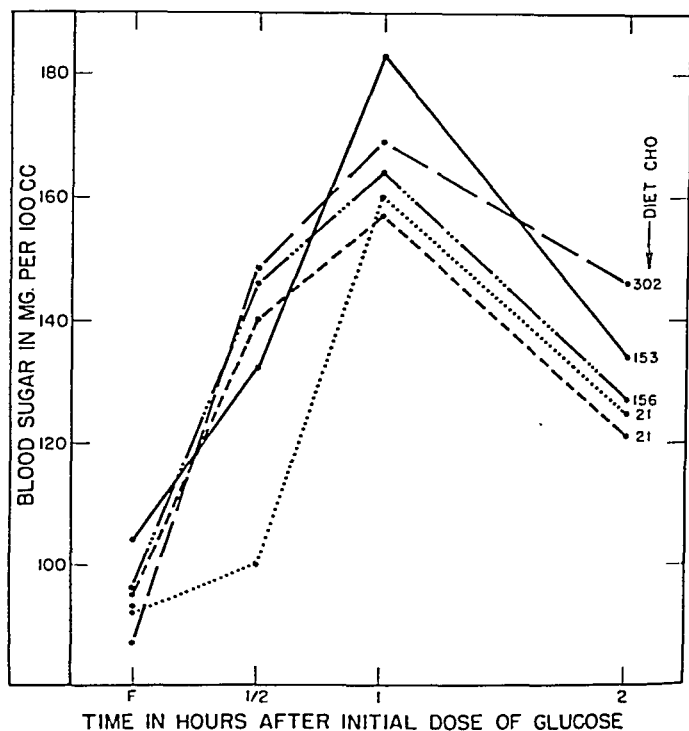


FIG. 5.—Blood sugar curves on Case 3.

TABLE 8.—TEST DIETS AND CURVES ON CASE 4; ARRANGED IN ORDER OF INCREASING CARBOHYDRATE CONTENT

Diet	CHO	Prot.	Fat	Cal.	Fast.	½ hr.	1 hr.	2 hr.
1	18	55	50	742	136	200	200	140
2	27	60	81	1077	127	200	222	198
3	182	70	7	671	129	179	174	105

CASE 4. Marked obesity, no glycosuria; a 52-year-old housewife whose complaint was obesity of marked degree dating from the menopause; she had been unable to reduce her weight on a diet of supposedly 1000 calories daily. After instruction in holding her diet to the level specified, she was placed successively on 3 sets of low calorie diets, with the results shown in Figure 6 and in Table 8. Despite the increased care there was no loss of weight. All 3 curves are abnormally high, but the best of the 3 is the one before which there was a liberal carbohydrate intake (incidentally, disproportionately low in fat). The fact that after the 27-gm. carbohydrate intake the curve is higher than after the 18 must be attributed to the vari-

ability of the individual, inasmuch as the two diets are sensibly identical in both carbohydrate intake and carbohydrate-fat ratio. Again it may be emphasized that the absolute amount of fat in the diet does not influence the blood sugar curve.

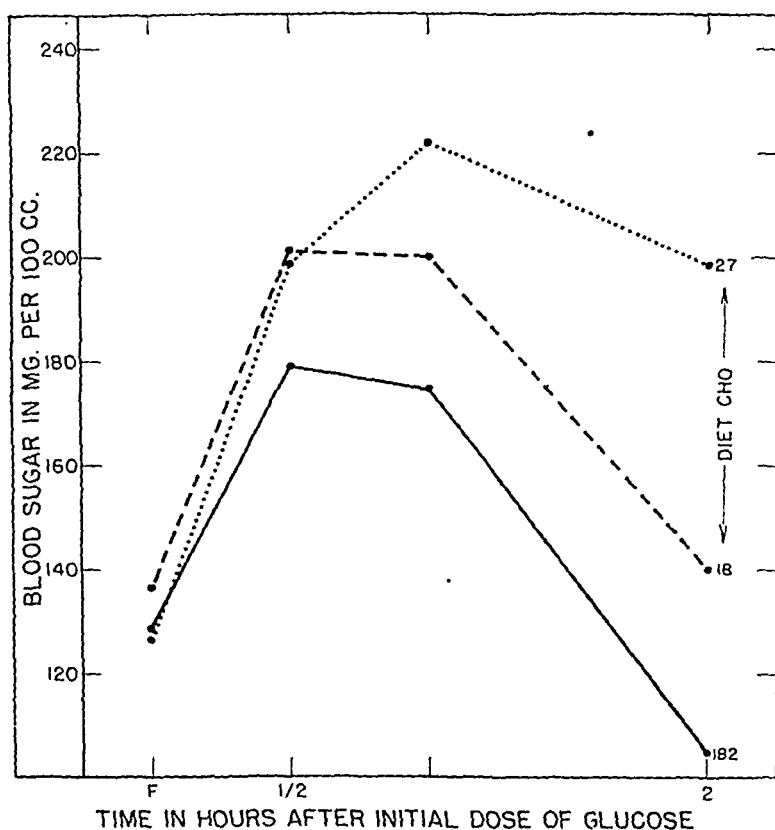


FIG. 6.—Blood sugar curves on Case 4.

CASE 5. Mild obesity; a 26-year-old married female clerk whose obesity was mild and who also had asthma and recurrent herpes simplex. The weight was 137. She was placed on a series of low calorie diets with results outlined in Figure 7 and Table 9. There was moderate loss of weight.

TABLE 9.—TEST DIETS AND CURVES ON CASE 5; ARRANGED IN ORDER OF INCREASING CARBOHYDRATE CONTENT

Diet	CHO	Prot.	Fat	Cal.	Fast.	½ hr.	1 hr.	2 hr.
1 . . .	25	60	80	1060	78	150	121	84
2 . . .	30	Low	89	137	93	92
3 . . .	180	56	7	907	93	134	93	101

It is to be noted that Diets 1 and 3 were nearly equal in total calories and in protein content, but were completely opposite with regard to the ratio of carbohydrate to fat, while Diets 2 and 3 were almost identical, whereas that resulting after Diet 1 showed a higher curve than either. All three curves indicate normal carbohydrate utilization, again independent of marked fluctuation in the test diets, once more supporting the thesis that superiority lies with the 2-dose load.

Comment. *Carbohydrate Content and Human Variation.* The expectation that decreases in the carbohydrate intake progressively damage the blood sugar curve in the 2-dose glucose tolerance test is supported only by Case 1. The results obtained in the other 4 patients, with a variation in the carbohydrate intake from 18 to 302 gm., suggest a lack of dependency on the diet, and serve to emphasize the importance of considering the extent of human variability. All of the curves in all of the patients except Case 4 lie within the zone of two standard deviations plus or minus from the means of the 35 normal cases examined by us previously.

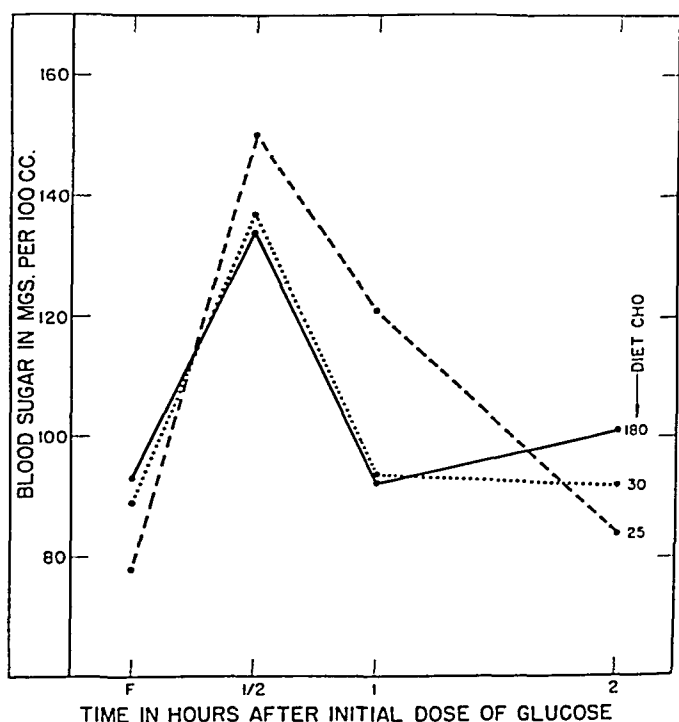


FIG. 7.—Blood sugar curves on Case 5.

This amount of variation indicates that many of the results commonly considered statistically significant may have been due to chance.

Superiority of the 2-dose Test. Sweeney, Muirhead and Allday¹² placed groups of 2 to 6 normal young adults on diets composed exclusively of one or another of the different foodstuffs for 48 hours (*i. e.*, 2 days and not 2 weeks as in our studies) preceding the 2-dose test. They found that such abnormal antecedent diets distort 2-dose curves less than the single-dose test, and that the distortion is relatively less at the end of 2 hours. Their findings are extended

by the results obtained in our patients. It is noteworthy that in 4 out of 5 of our cases the level of the $\frac{1}{2}$ -hour blood sugar decreased progressively with the increase in the dietary carbohydrate and that in the 5th case the points were around the same level. This $\frac{1}{2}$ -hour specimen may be regarded as an index of the 1-dose load.

Uniform Antecedent Diet. Conn² has emphasized the importance of a diet of uniform composition before any tolerance test is performed. The diets given to our patients were followed for a period of 2 weeks so that the question of duration of the preceding diet cannot be raised. It is freely admitted that the composition of the food ingested may not have been exactly that which was prescribed but we believe that the actual diet was closer to that prescribed than is ordinarily the case. The important fact from the practical point of view is that within the limits of the average free diet the amount of carbohydrate ingested does not significantly alter the interpretation dependent on a glucose tolerance curve in the 2-dose test. The dietary factor may become important when the patient is on certain special diets.

The significance of the differences in the responses of the single-dose and double-dose tests after variations in the preceding diet derive from the phenomenon that the first dose of glucose acts rapidly to produce the same desideratum as a uniform antecedent diet, namely a constant balance preceding the second dose. Physiologically, it seems likely that this uniform procedure results in packing the liver with glycogen which becomes quickly available for breakdown into glucose, and perhaps causes production of insulin at a more constant rate.

Conclusion.* The 2-dose glucose tolerance test is relatively free from the influence of fairly marked changes in the composition of the preceding diet. It is thus free from the confusion associated with the single-dose glucose tolerance test and is therefore superior when the antecedent diet is not known, as is usually the case. These differences in the two types of tests are dependent on the fact that the first dose of glucose acts as a constant balancing portion of the diet preceding the second dose.

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PYRUVIC ACID METABOLISM IN DIABETES MELLITUS*

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It has recently been demonstrated that in normal individuals the ingestion of glucose is followed by a rise in blood pyruvate.² This elevation almost invariably reaches a maximum at the end of 1 hour (Fig. 1) and returns to the normal fasting range within 3 hours. In conditions associated with thiamine deficiency, the fasting blood pyruvate is elevated^{3,4,6,7,8} and the pyruvate curve following glucose ingestion is abnormally elevated and prolonged² (Fig. 2).

The present study was undertaken in order to determine the blood pyruvate curve following glucose ingestion in patients with diabetes mellitus.

Materials and Methods. Eleven observations were made on 10 moderately severe diabetics (requiring 30 to 52 units of insulin a day). The ages ranged from 9 to 82 years. The patients were free of complications except that 2 of the older patients had cerebral arteriosclerosis (A.F., Fig. 3, and R.F., Fig. 6) and 1 patient had peripheral neuropathy (G.A. Fig. 5). Insulin was withheld for 24 to 48 hours prior to the test. Glucose and pyruvic acid were determined in the blood with the patient under basal conditions. Immediately following this, 1.75 gm. of glucose per kilo of body weight were given by mouth as a 25% solution in tea. Blood specimens were taken at 30 to 60 minute intervals over a period of 7 hours, the subject remaining at rest in bed. At varying time intervals after glucose ingestion crystalline insulin was injected. Glucose and pyruvic acid were determined by methods previously used.²

* This work was aided by a grant from an anonymous donor for Research in Psychosomatic Medicine, the John and Mary R. Markle Foundation and the Williams-Waterman Fund of the Research Corporation.

BLOOD GLUCOSE (DOTTED LINE) AND PYRUVIC ACID (SOLID LINE) CURVES
FOLLOWING GLUCOSE INGESTION (1.75 GM. PER KILO).

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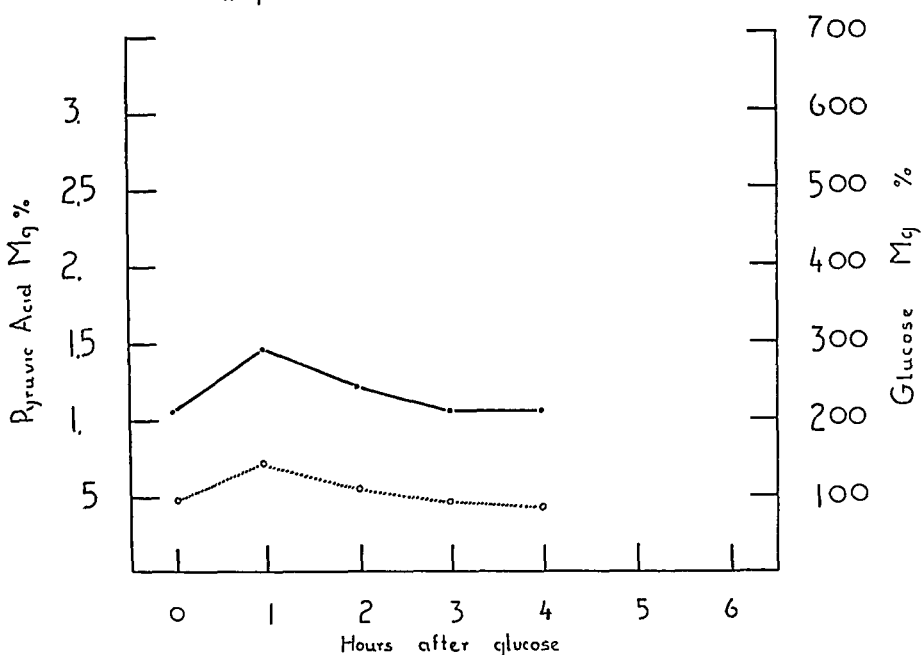


FIG. 1.—Average of 27 normal subjects.

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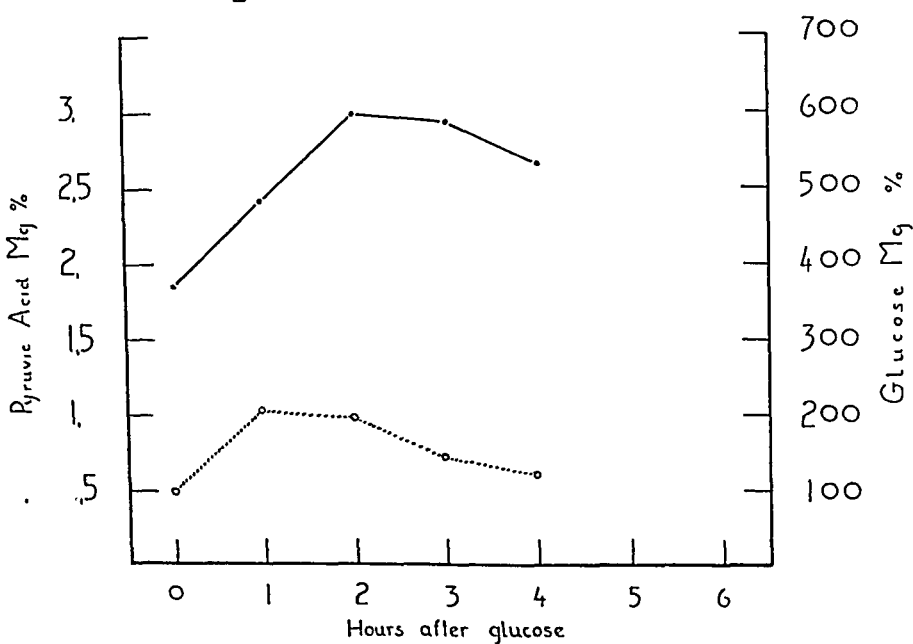


FIG. 2.—Average of 13 subjects with associated thiamine deficiency.

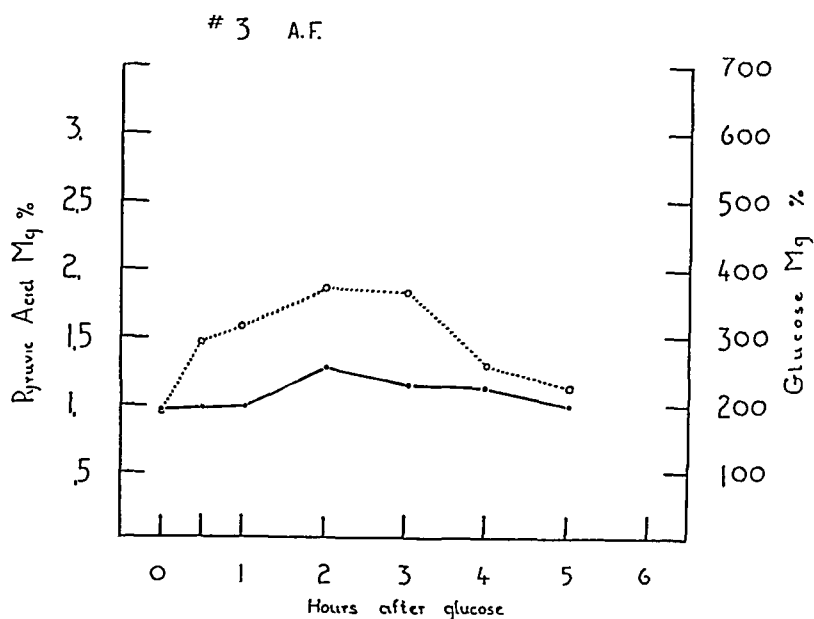


FIG. 3

FIGS. 3 to 12.—Patients with diabetes mellitus. The arrow indicates the point at which insulin was administered. 7A and 7B are the results of experiments on the same patient. The experiment indicated in 7B (insulin given simultaneously with the glucose at the start of the experiment) was conducted 1 week after the initial experiment.

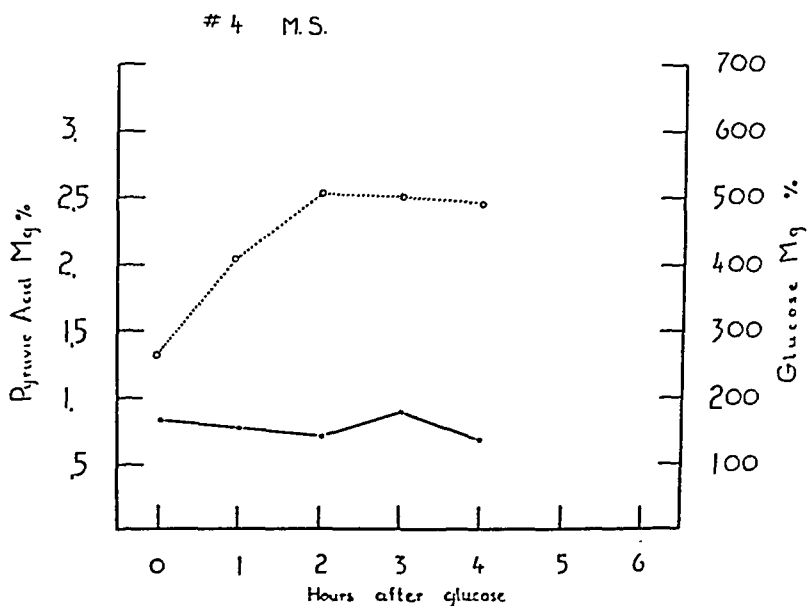


FIG. 4

Results.—As will be noted in the figures (3 to 12) there is little or no rise in blood pyruvate following glucose ingestion in patients with diabetes mellitus. The largest increases in pyruvate after glucose ingestion were observed in case G.A. (Fig. 5) requiring 30 units of

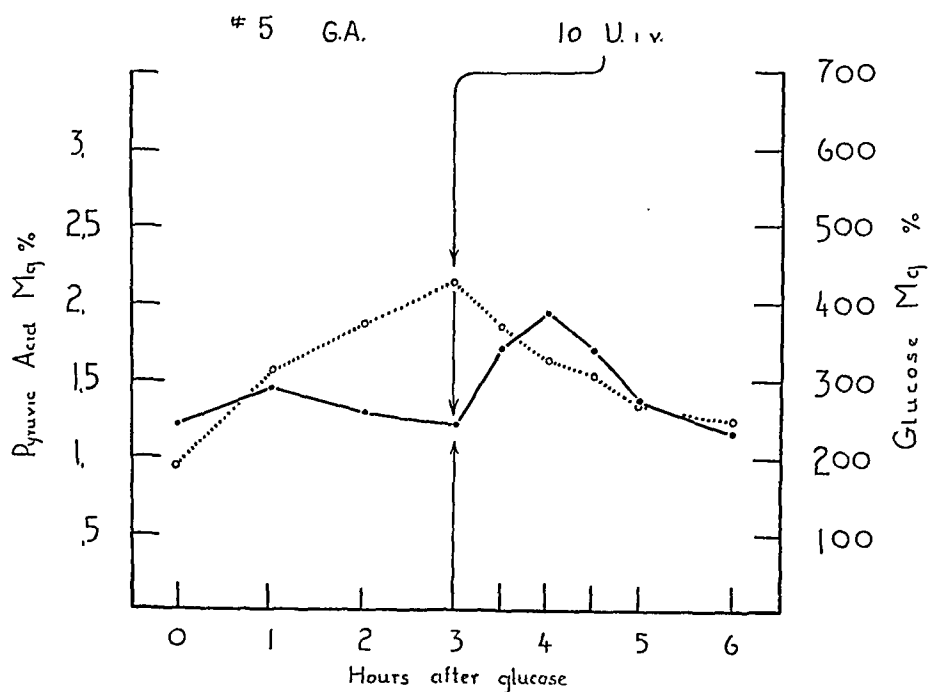


FIG. 5

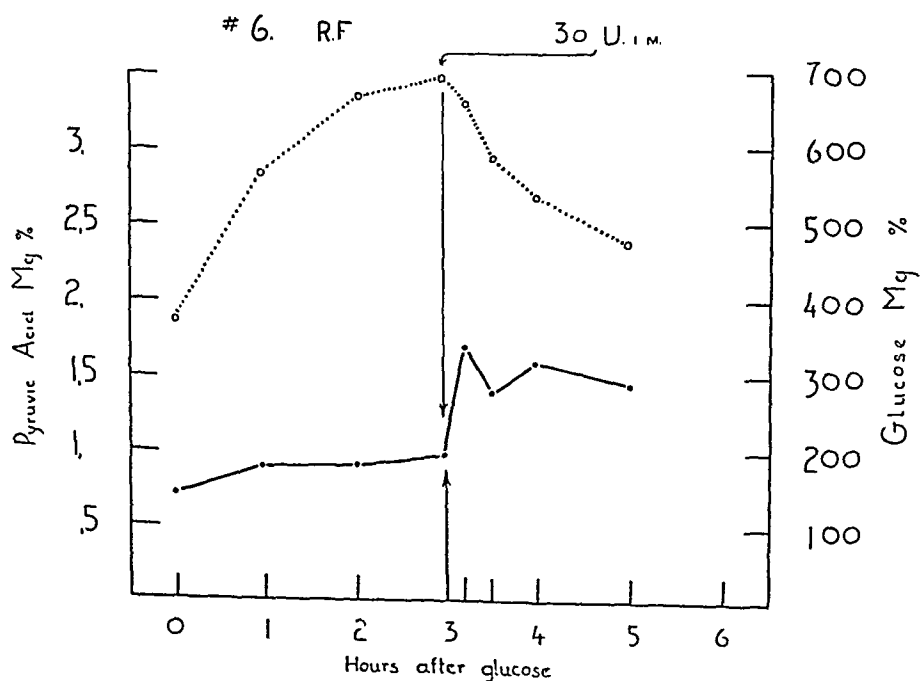


FIG. 6

insulin a day and having an associated peripheral neuropathy, and in case A.F. (Fig. 3) requiring 30 units of insulin daily. In every case of diabetes mellitus the rise in blood pyruvate following glucose

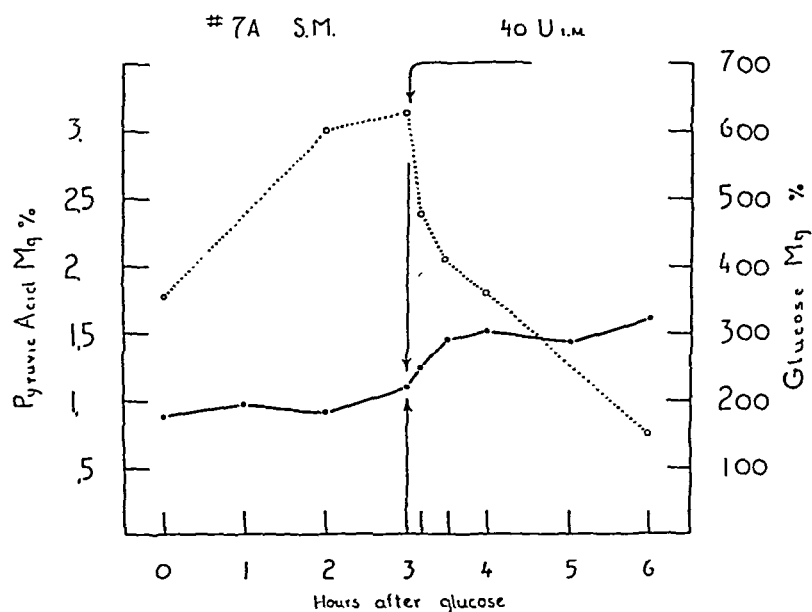


FIG. 7A

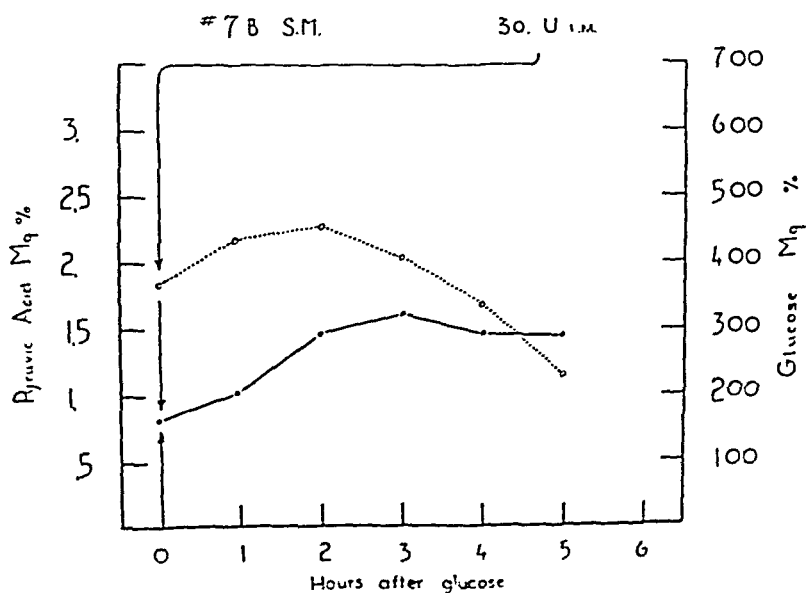


FIG. 7B

ingestion was smaller, and if an increase took place at all it had the tendency to occur later than in normal human subjects (Fig. 1).

Following the injection of insulin the blood pyruvate was significantly elevated in each case. This was true whether the insulin was given intramuscularly or intravenously.

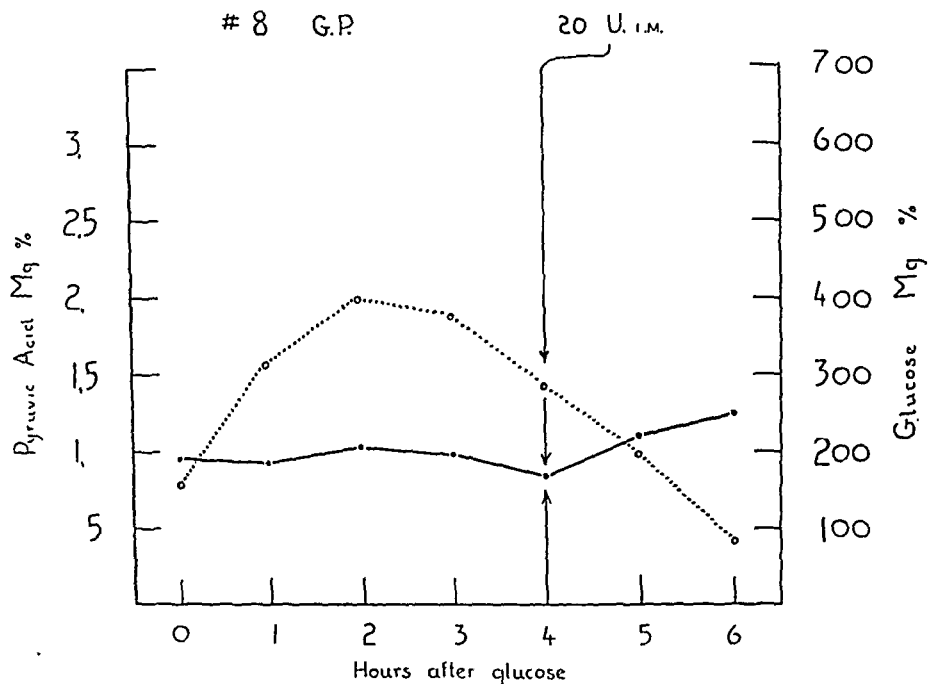


FIG. 8

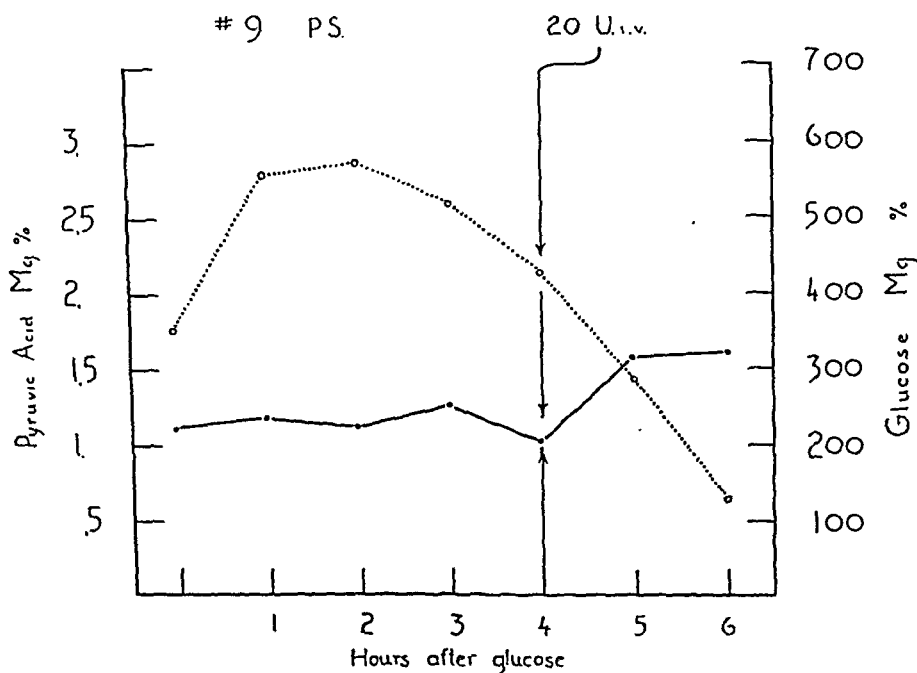


FIG. 9

These results suggest that the formation of pyruvic acid following glucose ingestion is increased by insulin. This received additional confirmation in a series of experiments on depancreatized dogs.¹ In

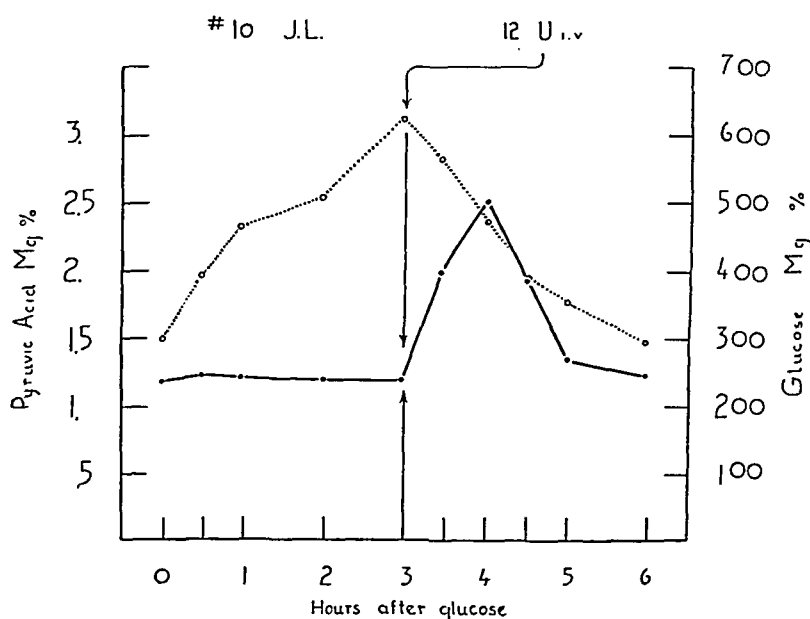


FIG. 10

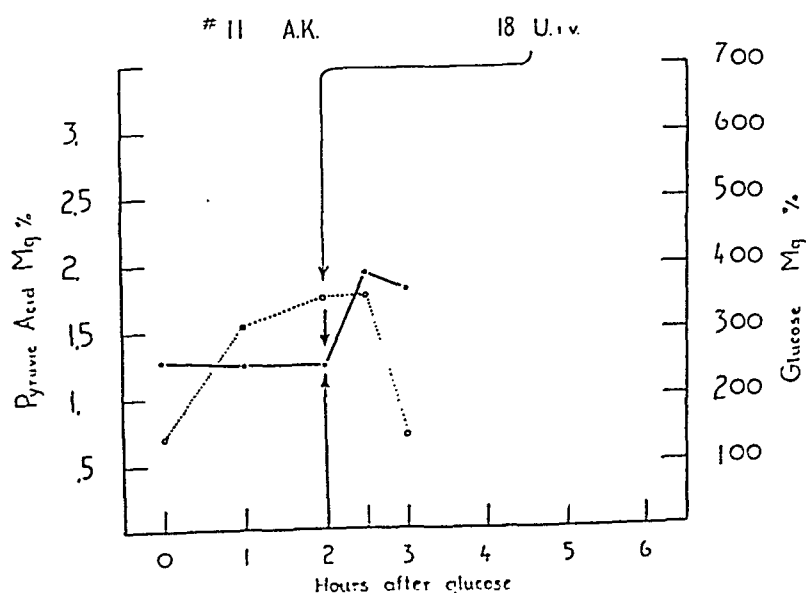


FIG. 11

these animals the intravenous injection of glucose was not followed by any rise in blood pyruvate unless insulin was supplied to the animal. In normal dogs, on the other hand, the injection of the same amount of glucose was followed by a significant rise in blood pyruvic acid. In addition, the rate of removal of intravenously injected pyruvic acid is the same in the normal and the depancrea-ized dog.^{1,5} This suggests that insulin increases the formation of pyruvic acid after glucose administration, and has little or no effect on the rate of removal of this substance.

Previous work has shown that thiamine pyrophosphate is important in the removal of pyruvic acid, and the present study indicates that insulin is of importance in the formation of pyruvic acid following glucose administration.

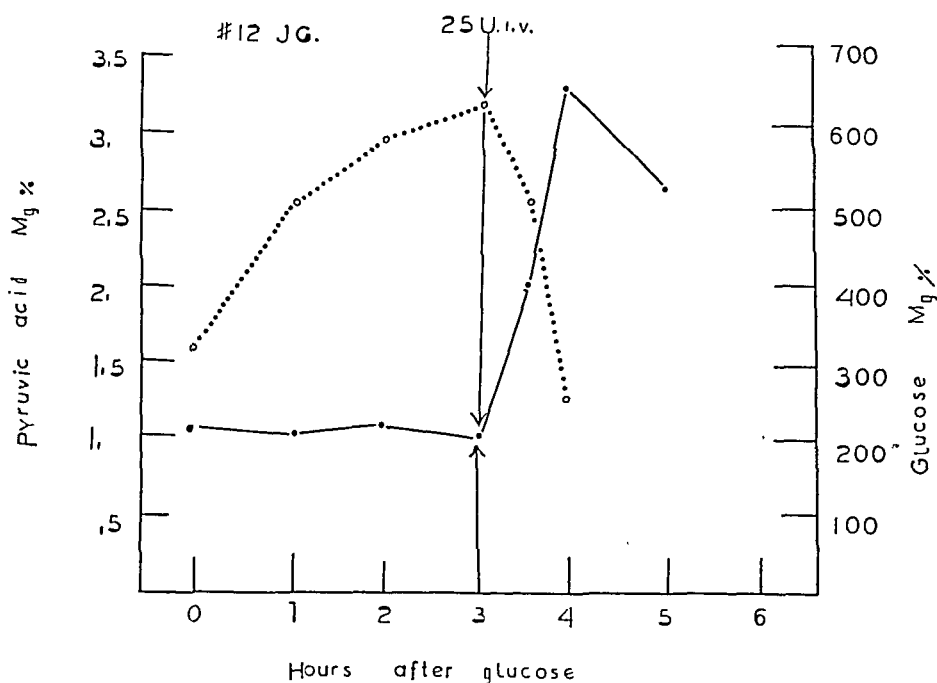


FIG. 12

Summary. In diabetes mellitus there is little or no increase in blood pyruvate following the ingestion of glucose. If insulin is then administered, a significant rise in blood pyruvic acid occurs.

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THE RÔLE OF PHYSICAL THERAPY IN THE REHABILITATION OF DISABLED SOLDIERS

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THE war has brought into relief many phases of medicine and surgery which, in turn, must be brought to a sharper focus to meet the exigencies of the moment. In many previous wars the number of soldiers invalidated by disease has exceeded those invalidated by missiles, and sometimes this disparity has been very great. World War I was indeed the first in which U. S. forces were engaged in which battle deaths exceeded deaths from disease:

DEATHS PER 1000 TROOPS PER YEAR

	Disease	Battle
Mexican War	110	15
Civil War (North)	65	33
Spanish-American War	26	5
World War	19	53

Modern warfare involves greatly increased incidence of trauma not only in the armed forces but also in the civilian population.

In general, casualties from disease begin earlier than do those from combat. Again, in general, the measures necessary to efficient therapy of the sick and of the wounded, respectively, differ rather sharply and do not greatly overlap except when complications occur.

There is, however, one field of treatment in war medicine which has wide application to both the wounded and the medically ill to an extent hardly shared by any other significant group of measures; namely, Physical Therapy.

This truth is appreciated by few of the profession, though many as army and naval officers, will see it exemplified. Much will depend, in terms of soldiers and sailors invalidated by trauma or disease, on the understanding which medical officers possess or may acquire of the principles involved.

It is commonly accepted that in civil life, employment of the beneficent influences of physical therapy has lagged far behind such understanding and utilization of them as are available. Many large industrial concerns, however, have for some years accorded to their employees every facility within the realm of physical therapy, with the aim of reducing the period of invalidism and returning the patient to productive employment at the earliest moment. Industrial medicine presents overwhelming data as to the success of this policy.

* Read by invitation before the General Scientific Session of the American Medical Association at Atlantic City, June 11, 1912.

What is the situation, however, in respect to that huge body of citizen soldiery, amounting eventually to perhaps 8 or 9 millions, which will constitute the armed forces of this country? To the great credit of the regular army, appreciation by it of the importance of physical therapy antedated World War I, and, by the same token, provision has now been made for equipment and trained personnel in the present crisis. The emphasis upon physical therapy in 1917-1919 afforded, indeed, the first significant introduction of the subject to the minds of the majority of medical officers. Fuller use of this field could have been made in those years had the members of the medical profession, inducted from civil life, been schooled to profit by the opportunity.

Orthopedic surgeons and, possibly, neuropsychiatrists, constitute in civil life the medical groups most cognizant of the irreplaceable nature of physical therapy in the fields of their specialties. The importance of the subject far exceeds those boundaries, however. Piersol¹⁵ pointed out before the Section on Medicine of this Convention a year ago the wide value of physical therapy to internal medicine in particular, as well as the relative unfamiliarity of most internists with it. Other groups in medicine have been strangely indifferent to the influences and results obtainable.

It seems relatively easy for those whose attention is turned for the first time to physical therapy to appreciate that the application of heat and massage to a fractured limb or articulation may have useful consequences. It seems more difficult, or at least more unusual, for such persons to realize that the same influences may have comparable value to dysfunctioning protoplasm in general, whatever the particular "solution of continuity" involved. Importance attaches, therefore, to directing attention, briefly, to some of the basic effects obtainable through physical therapy, to the end that the wide applicability of this field to a great variety of conditions may be more readily apparent.

Within the limits of the present contribution no full exposition can be made of the field as a whole, the conditions amenable to treatment or the techniques involved. These are available in great detail in several admirable treatises.^{4,6-8,10,14}

The central agencies of physical therapy consist of the quartet of heat, massage, rest and exercise. With the exception of radiation in the nature of Roentgen ray or from radium, little or nothing has been added, *i. e.*, new in principle, since the days of Hippocrates, though facility of application and improved techniques have made great strides. The above apparently simple quartet of measures may potentially influence nearly all bodily processes, directly or indirectly, and can be given either systemic or local application. It is vitally necessary for those whose function it will be to order or direct these agencies to know something of the mechanisms of operation concerned. The use of heat, for example, cannot be intelli-

gently applied without knowledge of what it accomplishes and the limitations involved.

The agreeable influence of heat upon an injured part is common knowledge and there is evidence, even to the layman, of hyperemia, characterized by redness. Heat from heated objects like bricks or hot water bags, may not be deeply penetrating. Heat can be made penetrating, however, by the use of modern techniques, such as diathermy. Whatever the source of the heat, capillary vessels are dilated and recent studies by Clark,³ utilizing a window in the rabbit's ear, have shown that an extraordinary increase in circulation may be developed, accompanied at certain stages by sticking of leukocytes to the vessel walls and eventual diapedesis into neighboring tissue. This observation is of great importance because it reveals the actual passage of particulate matter across the capillary wall. In the case of leukocytes this implies, by definition, phagocytosis and other influences which they exercise in the fixed tissues. It also implies, however, influences of a metabolic nature involving the basic physiologic processes of the parts concerned.

Systemic exposure to heat is shortly accompanied by a rise in body temperature, accompanied in turn by an increase in the heart rate of about 10 beats for each degree of fever. This rise in cardiac rate is accompanied by peripheral vasodilatation. There takes place a great increase in the rate of circulation throughout the body as a whole and many tissues share something of the influence following exposure of a part locally, the net result of which is an increase in total metabolic activity. Sweating is induced as a means of combating the rising temperature. Hyperventilation also develops, resulting in further loss of heat by evaporation. Coincidentally, there is a loss of carbon dioxide through the lungs, sweat and urine, though probably few medical men realize that the skin and kidneys also provide for removal of this end product. The net result of the loss of carbon dioxide through the lungs, sweat and urine, is a relative alkalosis of the blood and fixed tissues. This alkalosis constitutes a limiting factor in the extent to which exposure to heat can be pushed, since tetany may develop. This is one of many possible consequences occurring during the induction of artificial fever or hyperpyrexia. This last-mentioned form of therapy is of proven value in such conditions as gonorrhea, undulant fever, syphilis, and certain other conditions but is limited to institutional use. The gentler uses of heat, either local or systemic, short of this extreme form of application, have far wider exemplification, especially under conditions of warfare, and offer fewer dangers. In both the local and systemic use of heat the lymph channels are affected and the lymph flow is accelerated.

It must be apparent that any measures exercising such reparatory responses as heightened blood and lymph flow, phagocytosis and increased metabolism must influence a wide variety of pathologic

conditions, ranging from trauma and infection to many disease states at large.

The use of heat locally, and sometimes systemically, paves the way for the second of the quartet of measures constituting the main field of physical therapy; namely, massage. There should be pointed out the fact, ordinarily lost sight of, that about 25% of the blood of the body is in the capillary beds. Many of these beds are near the surface or at the periphery and, directly or indirectly, are available to physical influences. Curiously enough, the profession has had some anatomic but apparently very slight physiologic acquaintance with the capillary beds of the body. It is, however, only in and through these systems that the vital processes of living take place. The larger vessels of the body serve no purpose other than affording passage of the blood to those capillary regions at which its functions of oxidation and nutrition can be exercised. The capillaries and arterioles respond to both nervous and physical stimuli and the ordinary phenomenon of blushing illustrates the intimate connection between the capillary beds and the sympathetic nervous system. By the same token, drawing the finger nail across any skin surface is accompanied by a narrow line of blanching, followed by redness, which illustrates a combination of physical and nervous influences upon the underlying vessels. That this influence is susceptible of valuable directional application on a larger scale has failed of adequate recognition. Study of the rabbit's ear³ has shown that light stroking of capillary beds induces changes, somewhat comparable to those following heat, in the caliber of the capillary vessels, the rate of blood flow through them and other phenomena such as migration of leukocytes. The extent and duration of these changes depend upon the vigor of application of the stimulus. Stroking is, in part, a light variant of that "laying on of hands" which constitutes the practice of massage, and in the full use of massage it is evident that muscle tissue and even certain organs can almost be seized as a whole. Some cellular and acinous contents of certain organs can be expressed or changed in respect to their distribution.

Massage seems to partake somewhat of the nature of exercise and is often regarded as a substitute for it. It is not a substitute, however, and there is none. There are certain advantages in this from the fact that, in contrast to exercise, there is no production of lactic acid following massage such as accompanies the voluntary use of muscle. Neither is there any production of alkalosis such as follows exposure to heat. Massage is thus devoid of either of these consequences even though administration of it be prolonged and severe. Advantage is taken of this fact by trainers of athletes and even horses in that recovery from severe exercise may be definitely expedited by the skillful use of massage.

By the same token extravasations of blood or débris into tissue

from trauma can be removed much more rapidly than would otherwise occur. This influence is inadequately utilized and has also application to a wide range of medical conditions characterized by metabolic or other kinds of detritus. This is conspicuously true of conditions accompanied by an excess of tissue fluids. The pitting which develops under pressure of the finger on the pretibial regions in cardiac decompensation is an example of displacement of fluid which can be taken advantage of, when applied systemically over a large area, to restore fluid toward the vascular channels through which alone it can be removed.

Finally, there is an influence of massage upon the peripheral blood count which has had scant recognition, and is easily demonstrated by a stick of the finger. Following general massage the blood count may be significantly higher. Many capillaries are normally closed and red cells in stagnant, inactive regions may be returned to the general circulation under the stimulus of massage. A slight rise in the oxygen content of the blood can be demonstrated at the same time and there often takes place a definite diuresis.² The influence of one exhibition of massage upon the red cell count is ephemeral and small, but the cumulative effect of repeated induction probably accounts for some of the striking benefits inherent in a sustained course of massage. These influences obtain even in the presence of anemia,¹¹ and it is probable that this important relationship has not yet been fully exploited.

There are undoubted limitations to the use of massage in anemic or edematous states, but extensive use of it in the syndrome of arthritis has thoroughly demonstrated that, properly given, it can be exhibited with entire safety and conspicuous benefit in these directions.

From what has preceded, it is axiomatic that heat and massage, should have value in the treatment of trauma. Trauma induces cellular death with variable damage to capillaries and lymphatics. If hemorrhage into tissue occurs there arises irritation from broken-down blood constituents. With increased tension from swelling, interference with the finer circulation occurs which may go on to complete block and tissue death from this cause. A fibrous network is formed which can be digested and carried off so long as it is fibrin. Within a few hours, however, fibroblasts begin to grow and newly formed connective tissue leads to thickening and loss of elasticity. Elevation of the part, gentle stroking, sedative massage, and low heat for prolonged periods may be very valuable in avoiding early organization. All of these influences must be considered quantitatively as well as qualitatively. Intense heat, massage causing pain, exercise causing distress, will only intensify local stasis.¹²

Many powerful therapeutic agencies are two-edged swords and cut both ways. This is particularly true of massage. It may be used to direct blood to tissues greatly needing it. Improper use of it may

draw blood away from regions greatly needing it and so lead to fatigue and depletion. The statement can be confidently made, however, that any far-flung system of therapy directed at large numbers of soldiers and civilians which pays no heed to the rôle of the peripheral capillary beds in such conditions as arise out of warfare falls far short of the best theory and practice of medicine.

Attention should be turned briefly to that member of the quartet constituting physical therapy coming under the head of exercise. As already mentioned, exercise, either local or systemic, is eventually accompanied by an acidosis due to the production of lactic acid by the contracting muscles. In contrast to the influence of massage, exercise affords the only means of developing muscle although it is true that massage will add greatly to the tone and firmness of muscle. During exercise the heart rate is accelerated, the circulation of the blood is increased, sweating may be induced and some of the phenomena in the capillary beds discussed under heat and massage may be brought about. The availability of these influences to the sick and wounded from active exercise is of course negligible. There usually comes a time in the use of massage upon the locomotor system, however, at which voluntary exercise becomes necessary in order to carry to a further point the reparatory processes inaugurated. One phase of exercise coming to be known as "postural exercise" requires mention. This involves deep breathing, achievement and maintenance of better posture and even the assumption of proper or "hyper-physiologic" postures in recumbency. These measures go far to compensate for loss of bodily activity and have great value for persons confined to bed or a sedentary life. The several series of measures under discussion can obviously be coordinated, and also tie in closely with the topic next to be discussed, namely, rest.

Rest is as important in the exhibition of physical therapy as in the treatment of cardiovascular conditions or pneumonia, but rest is not the simple negation of activity popularly connoted by the term. The resting phase of muscular activity is an integral part of muscular activity. Only trainers appreciate this relationship in its entirety. Systemic rest accomplishes specific purposes which no other measures can bring about and should be so carried out as to promote these ends. Rest in recumbency has the following consequences: 1, The avoidance of excessive blood flow to active areas permits of dilatation of capillaries elsewhere and the determination of blood to such regions; 2, this promotes even distribution of blood throughout the capillary beds; 3, the warmth of the bedclothes may further open up peripheral capillary beds; 4, these influences permit passage of tissue fluids into the vascular channels; 5, rest permits relaxation of the nervous system by releasing it from the maintenance of muscular tone; 6, allows ptosed and dysfunctioning organs to assume normal positions and functions; 7, reduces the metabolic

load because the lowered energy outgo permits a lowered energy intake; 8, permits replacement of the metabolic deficiencies and removal of the surfeits constituting fatigue; 9, by removal of static strains, rest permits subsidence of inflammatory processes and enables the process of repair to succeed.

These influences of rest underlie in principle reparative processes in all tissues and are not to be regarded as limited to any one condition. It would be well if the various components of rest could be prescribed separately for the specific purposes which they achieve rather than under a blanket prescription such as the term usually connotes. In the complicated syndrome of the arthritides, specifically directed rest may have brilliant exemplification and much has been learned by refined study of it in these states.

Time has been taken to stress the apparently simple but basic aspects of physical therapy, because the field as a whole has often been regarded "mechanistically" and has been associated in the mind of practitioners with apparatus of many kinds. Furthermore, there also exists the impression that such measures have application to a few conditions only, whereas the truth is that the physiologic influences discussed, whether achieved by Nature alone or with assistance, underlie rectification of dysfunction in almost the whole of medicine and much of surgery.

As remarked earlier, it would be impracticable to include here enumeration of the traumatic and surgical accidents in which physical therapy is chiefly of value. Suffice it that these are almost legion and that rehabilitation of various types of orthopedic cases bulks large in this field. According to Krusen,⁸ "The surgical lesions most amenable to treatment by physical therapy under conditions of warfare fall into two general categories: (1) trauma of bones and joints, including fractures, dislocations, stiff joints, bone grafts and traumatic arthritis, and (2) trauma of soft tissues, including scars (especially of amputation stumps), contusions and lacerations of muscles and tendons, postural strains (particularly backache and flat foot), paralysis and tendon transplantations." Goldthwait⁵ has well said, "An operation upon a bone or joint may be technically most perfect, but unless measures having to do with restoration of function are instituted as soon as possible after healing a result that might have been perfect may, from the point of view of function, be very poor."

In the treatment of fractures, physical therapy is of immediate and irreplaceable importance. To quote Wilson,¹⁶ the indications are: "First, restoration of anatomic form as soon as possible; second, maintenance of alignment and fixation of the fracture; third, institution of measures to overcome circulatory disturbance and to maintain and develop function beginning at the earliest possible moment." "The only measures capable of accomplishing this purpose belong to the domain of physical therapy and should

be included just as regularly in the treatment of fractures and employed with the same skill as are reduction of the fracture and splinting to maintain alignment."

Shock is a frequent consequence of severe trauma. The most effective treatment of this condition includes two of the basic influences of physical therapy; namely, rest in recumbency and the application of external heat. It might be suggested that in view of the peripheral circulatory collapse accompanying shock, conservative application of effleurage and massage might, in certain cases, facilitate the venous return of fluid through the vascular system by reducing stagnation in the capillary beds.

Physical therapy in conjunction with occupational therapy is also of prime importance in rehabilitation of individuals subjected to amputations, dislocations or injuries of peripheral nerves.

Because of the influences of physical therapy upon normal physiologic processes, many medical conditions are also benefited thereby.

The medical states in which physical therapy has its greatest value can be enumerated in approximately the following order:

1. Arthritis, rheumatism, fibrositis, neuritis and muscular conditions constitute a field in which physical therapeutic measures experience some of their most brilliant consequences. In this connection there is a calculated incidence of at least 100,000 cases a year of rheumatoid disability for an Army of the size at present contemplated. The value of physical therapy to the orthopedic manifestations of the arthritic syndrome is obvious but it has equal or even greater value to the syndrome as a whole, before deformity has arisen. The frequency of involvement of the peripheral circulation in the capillary beds in the arthritic complex affords obvious explanation of the value of heat, massage and rest to the tissues concerned.

2. A wide field of applicability of physio-therapeutic measures in general is to be found in disabilities of the nervous system, ranging from paralysis to the true psychoses. Weir Mitchell achieved world renown because of his treatment of various neurasthenic states on the basis of rest, massage and proper nutrition. That neurasthenic states, including psychic trauma, bulk large in warfare admits of no question and they probably also constitute part of the problem underlying so-called neuro-circulatory asthenia, sometimes referred to as the irritable heart of soldiers. It is to be doubted whether the full beneficial influences obtainable through physical therapy have as yet been adequately brought to bear upon this syndrome.

3. The next most frequent group of diseases to which physical therapy is applicable under war conditions falls under the general head of cardiovascular conditions. Some of the most famous spas of Europe, such as Nauheim, have directed their facilities chiefly to the field of cardiovascular disease. Wide use has been made there

of warm baths, massage, resisted movements, graduated exercise and conditioned rest. The results of these measures leave no doubt as to the benefits to be achieved, and have been emulated throughout the world.

4. Another exemplification of the same principle is to be seen in the use of heat, massage, and the so-called vascular boot to peripheral disease of the blood-vessels. While the disease states falling under this category find their most frequent incidence in the later years of life, conditions of warfare and such diseases as diabetes nevertheless introduce parallel problems which must be handled in a comparable manner.

5. In many previous wars, typhoid fever played a large rôle in the disablement and death of soldiers. In the present war, as in the last, typhoid fever will probably occur to a negligible extent because of prophylactic vaccination. There still exists, however, in Europe at least, the scourge of typhus. While prophylactic measures have apparently some value in typhus they are by no means always infallible or available and it is to be expected that any army occupying the East Central Europe will be exposed to typhus. In this event it is probable that the Brand bath could again have wide application. One of the most brilliant examples of the application of physical therapy to flamboyant, febrile disease is to be seen in the application of the cold bath, with friction from massage, to the heavily toxic typhoid state. The sordes, coma vigil, subsultus tendinum, peripheral stasis, lividity, and other symptoms are largely referable to the impaired circulation, especially in the peripheral capillary beds. The change from this state, properly called typhoid, or typhus-like, to that of a calmer nervous system, clearer mentality and improved circulation, constitutes, at times, as dramatic a contrast as medicine has to offer.

Another phase of warfare cognate to purely military activities themselves, though not partaking of them, is that developed under conditions of bombing. In London,¹³ occupation of underground shelters has definitely increased the incidence of arthritis and rheumatoid conditions. There is also an increase of peripheral palsies, of the arm, for example, induced in persons who fall asleep in awkward positions because of exhaustion. Physical therapy has been one of the measures upon which chief reliance has been placed in caring for these victims of the war.

The final category to which attention should be called is that of convalescent states in general in which the indications and opportunity for the use of physical therapy are so numerous and widespread as to make enumeration impossible.

From whatever standpoint the question is viewed the exhibition of physical therapy in the care of the disabled soldier is, within the limits of its applicability, coequal in importance with purely surgical or medical procedures, and often exceeds either procedure. Physical

therapy should indeed be regarded as part of the fields of medicine and surgery and any separation of it from them is artificial. The excuse for considering it a separate phase of therapy is the fact that, as a field of therapeutics requiring special study and training, it is hardly more than a catchword to many physicians and still needs to be explained and emphasized. A deplorable situation exists in civil life which now permits hosts of traumatized and medically ill persons to become permanently invalided because adequate facilities and trained personnel are not available, or because their medical advisers are not adequately cognizant of the remedial potential in the field under discussion. Much the same limitation to optimal physical therapy will be present in the army unless adequate emphasis is given the subject in the minds of inducted medical officers.

The proper prescription of physical therapy requires familiarity with the physiologic influences operative and with clinical application of them. This is the obligation of the physician or surgeon. The proper conduction of physical therapy is the obligation of the trained physical therapeutic technician. Unfortunately, technicians are limited in numbers, and time is required to train more. By the same token, physicians qualified to prescribe physical therapy, not to say carry it out, are even fewer. Indeed, the ironical situation exists that physical therapeutic technicians, supposedly operating under direction of the profession, may be actually more familiar with the indications for physical therapy, as well as the technique, than are many of the profession themselves. Medical officers, inducted into the services, should equip themselves as to physical therapy in at least a preliminary way. Lowman⁹ has well said that the value of physical therapy in the event of another war (now upon us) will be determined not only by the work actually carried out by physical therapeutic technicians but also by the quality of the "prescriptive ability and intelligent interest shown by medical officers in charge."

Summary. The armed forces of the United States, in being and in prospect, will presumably reach numbers never before attained by this country. It is to be expected, therefore, that the number of casualties from trauma and disease will far exceed any figures heretofore experienced. Most phases of medicine and surgery having relation to the conditions under discussion will early experience wide development and application. This cannot be said with equal confidence, however, of that field of treatment known as physical therapy. Notwithstanding the demonstrated influences of physical therapy upon normal and deviated physiologic processes, appreciation of these influences is not yet sufficiently widely disseminated, throughout the profession as a whole, to assure that physical therapy can automatically take its place alongside of surgery and medicine with the expectation that proportionately good results will be achieved.

Those of the profession entering the armed forces should acquaint themselves with these influences and learn on a larger scale than obtains at present when to prescribe the measures under discussion. Such measures should be carried out when possible by physical therapy technicians. There will be sharp limitations, however, to the personnel available to do this and a conscious effort must be made to atone for this gap by application, on the part of medical officers themselves, of at least some of the simpler practices of physical therapy. Given the state of medical preparedness as it now exists, there is probably no other field of medicine in which early and full grasp of the principles at stake would have equally significant results in terms of returning men to duty and in reducing invalidism.

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STUDIES OF BIOTIN METABOLISM IN MAN*

PART I. THE EXCRETION OF BIOTIN IN HUMAN URINE

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As early as 1929 it was suggested by Findlay and Stern¹⁰ that certain skin and nervous system changes in children, known as Swift's disease or pink disease, might be due to a lack of some essential material in the diet. This suggestion was made because

* This investigation has been aided by a grant from the Josiah Macy, Jr. Foundation.

of the similarity between the clinical and pathologic changes in these children and those produced in rats as a result of feeding a diet of high egg white content. Although many years elapsed before the mechanism of "egg white injury" was clarified, the idea that a vitamin essential for man might be involved has been repeatedly mentioned. György, who gave the name vitamin H to the anti-egg white injury factor, has suggested several times that it might play a rôle in man.^{11,13,14} During the present year Sydenstricker, Singal, Briggs, De Vaughn, and Isbell²¹ reported that they had produced such a vitamin deficiency in man by egg white feeding and had cured it with a biotin concentrate.

The study of the factors involved in egg white injury in animals has been made principally by Boas,² Parsons, Lease, and Kelly,¹⁹ and György,¹² and their work has been recently reviewed by du Vigneaud.⁴ The universal biologic nature of the protective factor was indicated by the finding of du Vigneaud, Melville, György, and Rose⁶ that vitamin H is identical with coenzyme R, a respiration enzyme essential for the growth of *Rhizobium trifolii*, and biotin, a stimulant for the growth of yeast. Workers from these same groups later isolated the vitamin from liver.⁵ It now appears that the syndrome of egg white injury results from the formation of a heat labile compound between biotin and a substance in egg white¹⁵ called avidin,⁹ or antibiotin.²⁴ This compound is not absorbed from the intestinal tract and thus deprives the animal of biotin.⁸ This is the only condition under which rats have been made biotin-deficient, but chickens have been made deficient by a low biotin diet alone.^{1,16,17} Biotin-deficient chicks develop within a few weeks swelling and redness of the eyelids, cracking and bleeding of the skin of the feet and around the mandible, and loss of feathers. The skin lesions in the rat, which have a general similarity to those in the chick, have been regarded as a seborrheid desquamative type and they are accompanied by spasticity of the muscles and a kangaroo-like posture.

In the present study an attempt was made to learn something about the use of biotin in man by studying its metabolism. The work so far completed is reported in 3 parts. The first surveys the excretion of biotin in urine. The second gives data on the relationship between biotin intake and output, and the third describes and discusses the significance of a material with biotin-like properties which has also been found in the urine.

Methods and Results. The determinations were carried out by a yeast growth method described by du Vigneaud, Hofmann, Melville, and György (5). In this test a synthetic medium from which practically all the biotin has been removed is inoculated with a standard quantity of yeast culture, and 10 cc. amounts are added to 2 series of flasks. To one series known amounts of biotin are added, and the yeast is allowed to grow for 16 hours at 30° C. The amount of yeast growth in each flask is then determined by measuring its turbidity with a photo-electric colorimeter and from these

values a standard curve, or growth curve due to known amounts of biotin, is constructed. The second series of flasks is used to construct the growth curve for the substance to be tested. The biotin content of the unknown solution is calculated by simple proportion from the position on the growth curve of the unknown that corresponds to the point of half maximum growth on the standard curve. To form our standard curve, pure biotin was added in amounts of .1, .03, .01, .003, .001, .0003, .0001, .00003, .00001, .000003 micrograms per flask. The urine was added in amounts of .3, .18, .1, .056, .03, .018, .01, .003, .001 cc. per flask. These quantities of biotin or urine were made up to a volume of 2 cc. before they were added to the medium. Each 100 cc. of medium was inoculated with .6 mg. of 24-hour culture of *Saccharomyces cerevisiæ* strain 139.

When the biotin content of a urine was determined in this way the same value was found on repeated determinations. Twenty-four hour samples, collected in bottles to which 10 cc. of glacial acetic acid had been added, were found to contain the same amount of biotin after standing in the icebox for a month as on the day they were collected. There has been no evidence of biotin deterioration in any of the specimens studied. Neither was any of the biotin in urine found in the combined form in which it occurs in foods such as liver and yeast. In these materials biotin is present in a complex union from which it is separated only by autolysis, digestion, acid hydrolysis, or autoclaving. The urine value was not changed when the sample was mixed with concentrated HCl and evaporated to dryness or autoclaved 2 hours with concentrated H_2SO_4 .

TABLE 1.—BIOTIN ELIMINATION FOR NORMAL SUBJECTS

Subject No.	Micrograms per liter	Micrograms per 24 hours	Urine vol. in cc.
<i>Men</i>			
1	12 5	23	1810
2	46 7	44	950
3	12 7	24	1850
4	30 4	27	883
5	17 5	30	1700
6	7 8	23	2990
7	32 2	50	1560
8	23 4	26	1100
9	69 0	111	1620
10	39 0	41	1050
Variation	7 8-69 0	23-111	883-2990
<i>Women</i>			
11	89 1	46	520
12	20 4	48	2330
13	55 0	66	1200
14	44 6	49	1060
15	39 9	33	820
16	30 2	64	2120
17	28 2	39	1350
18	47 4	51	1090
19	64 6	106	1640
20	9 6	14	1500
Variation	9 6-89 1	14-106	520-2330

Other experiments were carried out to see if the material we were testing differed in any way from biotin derived from other sources. No difference was found except that only part of the material in the urine could be completely inactivated by egg white. The significance of this finding is discussed in Part III of this paper.

Most of the normal subjects excreted from 20 to 50 micrograms of biotin per 24 hours, but there were a few whose daily output was more or less than this. This is shown in Table 1, where the elimination by a group of 10 normal men and 10 normal women who ate their usual diets is listed. There was no significant difference between the average values for the 2 groups, and the range extended from 14 to 111 micrograms, with an average figure of 45.7 micrograms per 24 hours.

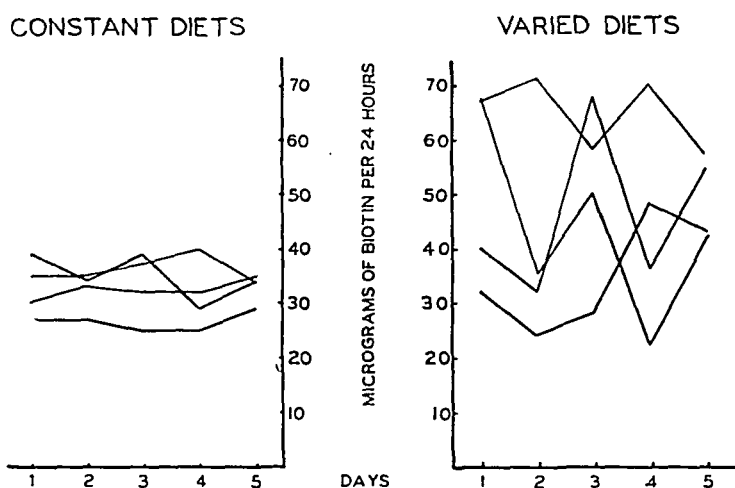


FIG. 1.—Biotin content of the urine of subjects who ate constant diets and varied diets for 5 days.

From day to day there was a moderate variation in biotin eliminated when the same subject ate an unrestricted diet. In contrast to this, there was little daily variation in the biotin content of the urine when the same diet was eaten each day. The opportunity to make such observations was provided by 4 patients who, because of various metabolic studies, ate the same diets every day for 5 or more days. In these diets not only the calories, minerals, protein, fat, and carbohydrate were kept constant, but the same breakfast, lunch, and dinner were eaten each day. In Fig. 1 the biotin excretion of these subjects on constant diets is plotted with the excretion values for a group of subjects who ate varied diets, and a rather striking difference is shown.

A study was also made of the elimination of biotin at different periods throughout the day. From 6 subjects on unrestricted diets the urines were collected so that the biotin excreted from one mealtime to the next could be measured separately. This value was divided by the number of hours between the collections of

urine, to obtain the average hourly excretion for the period. These results are shown in Fig. 2. The hourly excretion was usually, though not always, higher during the day than at night and was different for each subject. One hospital patient who received practically all her food for the day at 11 A.M. by stomach tube provided an ideal experiment for us. Her biotin excretion throughout the day showed a uniform pattern and was not increased immediately after the feeding. This is also shown in Fig. 2. The tube feeding she received contained the uncooked whites of 4 eggs, and we were interested to see whether these prevented the absorption of much biotin. The eggs were therefore left out of the feeding for 5 days but no significant change in the biotin content of the urine occurred.

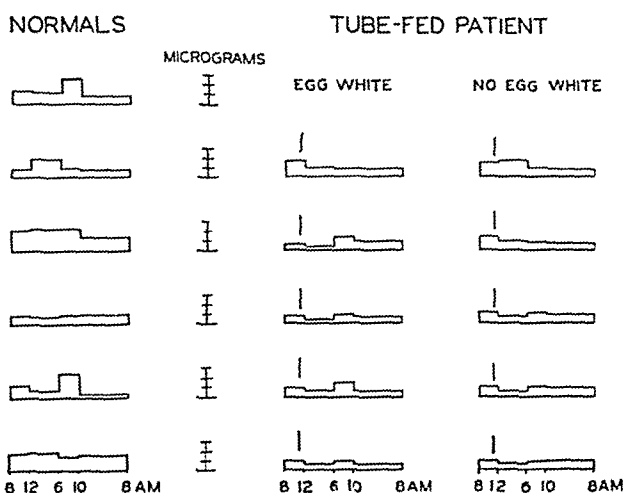


FIG. 2.—Hourly biotin elimination throughout the day. The area of each block indicates the amount of biotin eliminated during that period. The normals ate their ordinary meals. The tube-fed patient received her food at 11 A.M. as indicated by the line above each diagram.

When a test dose of crude biotin was taken by one subject there was a prompt flooding of the urine with it. A normal male, who usually excreted about 40 micrograms of biotin a day and who eliminated 3.18 micrograms per hour during the morning, drank an aqueous solution containing 1864 micrograms of crude biotin at noon. During the following 6 hours his urine contained 560 micrograms (93 micrograms per hour). During the 24-hour period after he took the biotin he eliminated 793 micrograms. These results are shown in Fig. 3.

The biotin content of the urines of 60 patients from the pavilions of the New York Hospital was studied to see if any of these showed a striking difference from the normal subjects. Cases with a wide variety of pathologic conditions were chosen, but those with skin or nervous disease processes were especially sought. Patients

with malignant disease, blood disorders, endocrine conditions, infections, and a variety of miscellaneous conditions were studied. An attempt was also made to find those whose food intakes had been

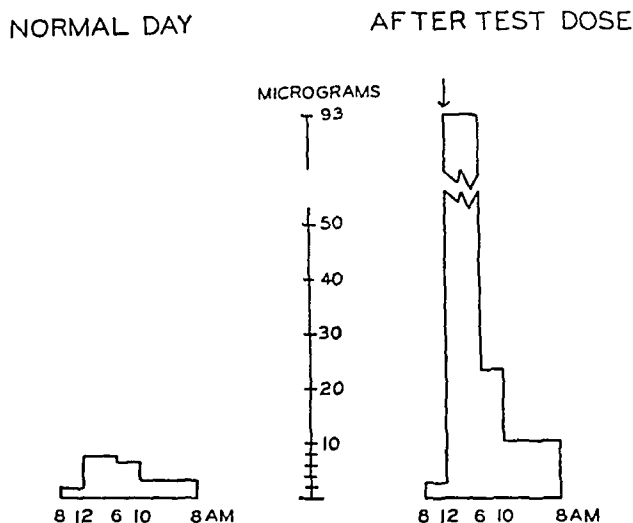


Fig. 3.—The effect of a test dose of 1800 micrograms of crude biotin on the hourly output in the urine. The arrow indicates the time of the dose.

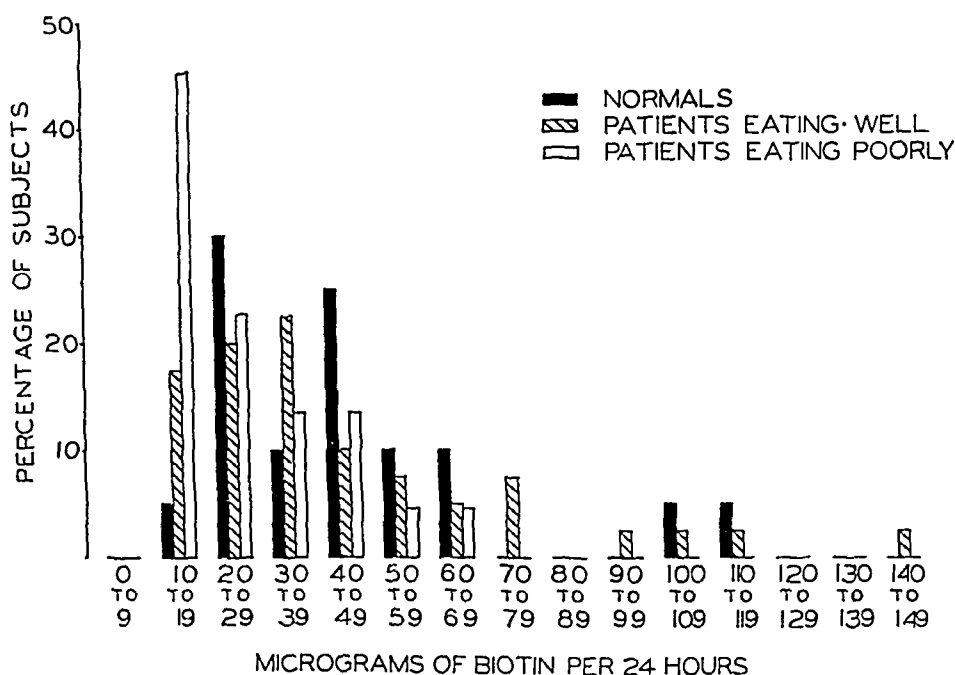


Fig. 4.—The effect of diet on the biotin content of the urine. Nearly 50% of the patients who ate poorly excreted only 10 to 19 micrograms of biotin per 24 hours.

greatly restricted by disease or treatment. Practically all the values fell within the normal range. In the majority of instances where the food intake of the subject had been conspicuously poor the biotin excretion values were low. This is graphically shown in Fig. 4,

where the biotin excretion values for the normal subjects, patients who ate well, and patients who ate poorly, are shown in separate columns.

Discussion. The conclusions allowed by these results are limited by the fact that our urinary biotin values can be related to biotin intake only in a general way. The amounts of biotin in so few foods are known that we cannot yet calculate its content in human diets. Isolated determinations of the biotin content of urine have been reported, but there has been no previous study of the significance of the urinary biotin. More specific information than we have here is gained from complete biotin balance studies, and such studies on human subjects are reported in the next part of this series. A few facts appear to be established from these results, however, and there have been some reports on biotin metabolism in animals with which they can be correlated.

There are 2 types of biotin metabolism in animals. Chickens are apparently dependent on their diets for biotin and become deficient when the supply is low. Eakin, McKinley, and Williams⁸ found that on ordinary diets these fowl excrete from 10 to 20% of their dietary biotin in free form and an additional 15 to 25% in a combined form which is liberated by hydrolysis. These figures represent the total biotin output since the excretion from the kidneys of these birds is present in their feces. It would appear that the rat is more difficult to make biotin deficient through ordinary dietary means than the chick, and he probably derives biotin from some other source than his food.⁴ Biotin from this non-dietary source as well as dietary biotin might be found in the rat's urine, but unfortunately studies of biotin excreted by rats have not been reported.

The experiments here reported clearly indicate that the biotin content of human urine is influenced by the amount of biotin in the diet. This is shown in several ways. When the subjects were grouped into those who ate well and those who ate poorly, a corresponding difference in biotin elimination was shown. For some individuals this did not hold true but there is no reason to believe that every large meal contains a large amount of biotin or that a small meal cannot. A correlation between biotin intake and urinary output is further shown by a comparison between the urine values of subjects who ate varied diets and of those who ate constant diets. In the former group the output is varied; in the latter it is quite constant. Moreover, the biotin content of urine was markedly increased by the ingestion of a test dose of crude biotin.

While the above experiments show that biotin in food affects the urine value, there are others that point to some source of the vitamin for man besides his food. Throughout these studies we have been constantly searching for a patient who excreted no biotin in the urine and we have analyzed the specimens of every patient we could find on a poor diet. Many of these were in the terminal stage of

chronic illnesses and had eaten nothing for days. In spite of this effort we have been unable to locate a patient without biotin in the urine. In fact, we have found very few who excreted less than our lowest normal. This is quite in contrast to other vitamin excretion studies and suggests that human subjects are not entirely dependent on food for their biotin. Evidence is presented in Part II of this paper to show that they derive a good deal of it from synthesis by bacteria in the intestinal tract.

In the study of patients we selected those who showed skin and nervous diseases since these body systems are the ones altered in biotin-deficient animals. Patients with malignant diseases were also investigated because of the findings, by other workers, of a high biotin content of tumor tissue²² and of the procarcinogenic effect of this vitamin.⁷ The rest of the patients were chosen to see if any alteration due to fever, anemia, increased metabolism, cirrhosis, or other abnormalities might influence biotin metabolism. No group of patients showed abnormally low values and only an occasional case excreted less than our normals. It cannot, however, be finally concluded that some error of biotin metabolism does not occur in these diseases. Such an error might be demonstrated by a more exact test than the determination of the biotin content of a 24-hour urine specimen, collected from a subject on an unrestricted diet.

Conclusions (Part I). In a study of the biotin excretion in human urine it was found that:

1. Normal subjects on unrestricted diets excreted from 7 to 89 micrograms of biotin (as measured by yeast growth stimulation) per liter of urine or from 14 to 111 micrograms of biotin per 24 hours.

2. With ordinary diets the biotin elimination varied from day to day, and throughout the day. There was a striking increase immediately after a large dose of crude biotin was ingested.

3. Biotin excretion was greater in the urine of those who ate well than in the urine of those whose intake of food was poor. It was relatively constant for those who ate the same food every day.

4. The biotin excretion of a large number of patients with a variety of disease conditions was studied. The values found were within the normal range and even during periods of starvation were not abnormally low.

PART II. THE RELATIONSHIP BETWEEN THE BIOTIN CONTENT OF THE DIET AND ITS OUTPUT IN THE URINE AND FECES

In Part I of this paper a general survey of the biotin content of urine was made and values for normal subjects were given. It was found that patients with a wide variety of morbid processes excreted relatively normal amounts of the vitamin. A general comparison of the abundance of the diet and the urinary biotin level was made and showed that the excretion was usually low when the

diet was poor. There appeared to be a level below which the value did not fall even during starvation. This low level was also reached, however, by some normals on a normal diet.

To investigate further the metabolism of biotin in man, balance studies have been made on a small group of patients. Most of these studies were done in the Metabolism Pavilion of the Russell Sage Institute of Pathology at the New York Hospital, and the routine of that Institute was generally adhered to, as described below. Nothing to date has indicated that the diseases for which these subjects were hospitalized or the treatments they were given created any disturbing effect on the experiments.

Methods and Results. To regulate the biotin intake each patient was kept on a constant diet and ate the same three meals throughout the balance period. Different subjects ate different diets and various combinations of diets were used. In the first series of experiments a constant diet was eaten every day. In a second series of experiments two diets of widely different biotin content were alternated. These latter diets were identical in the protein, fat, carbohydrate, calcium, and phosphorus content and the principal difference between them was that 50 gm. of liver and 110 gm. of steak were taken with alternate luncheons. After several days on either program, during which the collection of urine and stool specimens was begun, a dose of 0.2 gm. carmine was given and this was repeated at the end of the experimental period, which was usually 5 days later. In this way the stool specimens corresponding to the procedure previously outlined. The urines were analyzed by the procedure before analysis. A duplicate of the diets required considerable preparation before analysis. The day's food was thoroughly ground and suspended in water, and the mixture was shaken mechanically for 1 hour. It was then evaporated to dryness on a steam bath and the dry residue was ground and suspended in water to which 0.25 cc. concentrated H_2SO_4 was added for each 5 cc. of solution. This mixture was autoclaved at 20 pounds pressure for two hours, and then adjusted to pH 4 to 4.5, filtered with suction, and the filtrate made up to volume. Ten grams of the ground diet residue were made up to an ultimate volume of 100 cc.

The stool specimens for the whole period were mixed, dried, and hydrolyzed in exactly the same way as the diet except that 100 mg. of the ground stool were made to a final volume of 20 cc.

Because only a limited number of experiments of this type were feasible, certain refinements of the biotin analysis technique were made to increase as much as possible the accuracy of the results. In all cases the tests were run in triplicate so that an error of any single determination would be found. Furthermore, the specimens in each balance period were all analyzed on the same day so they could be calculated from the same standard curve. It had been previously found that on certain days the standard curve independently or sometimes with the unknown's curve, would not occupy its usual position on the chart. On such days the values were inaccurate. Errors of this type could be largely avoided by triplicate analyses and were probably completely avoided by using only those curves on which the standard fell within narrow limits, arbitrarily chosen.

The diets used are listed in Table 2. Diet 1 consisted of powdered milk and was found to contain 60 micrograms of biotin. When the hydrolysate of it was mixed with egg white in the proportions of Diet 1a, biotin activity was completely inhibited in the test tube. Diet 2 has a low calcium and phosphorus content but otherwise corresponds to the food consumed by

many individuals who are only moderately active. Diets 3, 4, and 5 are average, general diets, and the biotin values for them probably correspond to that of the average American diet. From the values found in these analyses, it appears that liver, which was present only in Diet 5, is one of the few foods which significantly alter the intake of this vitamin for the day.

TABLE 2.—COMPOSITION OF DIETS USED

	Diet No.					
	1	1a	2	3	4	5
Micrograms of Biotin	60	0*	30-34	34-37	32-35	54-65
Weight (gm.) { Wet	214	840	1212	1998	1873
Dry	1000	320	342	406	390
Calories	57	1543	2015	2014	2017
Protein (gm.)	60	55	75	75	75
Fat (gm.)	71	60	66	76	76
Carbohydrate (gm.)	185	283	246	246
Calcium (gm.)	0.1	0.6	0.9	0.9
Phosphorus (gm.)	0.6	1.0	1.3	1.3

* Diet No. 1 plus 18.3 gm. of powdered egg white.

The diet of powdered milk and egg white was given to 2 subjects, on one of whom it had to be discontinued after 2 days. She had previously finished a control period of 3 days on powdered milk alone. During these 5 days her biotin excretion values in the urine were 29, 31, 38, 33, and 20 micrograms. The other subject was not given a control period but took the milk and egg white combination 5 days, during which he excreted 30, 24, 36, 24, and 46 micrograms. These values were not significantly different from those he previously and subsequently showed on a general diet. The stools on these subjects were collected individually and varied so much in regularity, because of the constipating nature of the food, that they could not be compared with the other figures.

In all the rest of the experiments the results were much more satisfactory and were in general agreement. They are shown on Figs. 5 and 6 and on Table 3. Fig. 5 shows graphically the relative amounts of biotin in the diet and in the urine of two subjects on constant diets. Although these subjects ate different foods, they consumed approximately the same amount of biotin daily and each of them excreted a relatively constant amount in the urine. One subject excreted slightly less biotin than she consumed but the other excreted considerably more than he ingested each day. In other balance periods the urine not infrequently contained more biotin than the diet.

Fig. 6 shows the relationship between dietary biotin and urinary biotin when diets containing 35 and 65 micrograms were taken on alternate days. Under these circumstances the urinary biotin values were not constant as were those on Fig. 5 but showed daily variations which followed the fluctuations in biotin intake quite closely.

On Table 3 the figures for the biotin balance periods investigated are listed in detail. The daily intake in the diet and output in the urine is listed. The average daily value for output in the feces is given since all the feces put out during the balance period were mixed and analyzed together. In 2 cases where the urines were not obtained, only the diet and fecal values are given. It is at once evident from this table that the biotin content of the stool far exceeded that of the diet, and from three to six times as much biotin was eliminated in the urine and feces of these subjects as they could have absorbed from their food. Biotin synthesis by the bacteria in the intestine apparently furnished a reservoir from which biotin could be absorbed. There is some suggestion that a correlation existed

between the amount of biotin in the feces and the quantity in the urine. When Subjects B (Periods 3 and 4) and C (Period 1) consumed the same amounts of biotin, the stool and urine values of the former were both considerably higher than those of the latter. No correlation between the biotin content of the diet and that of the feces is suggested by these data.

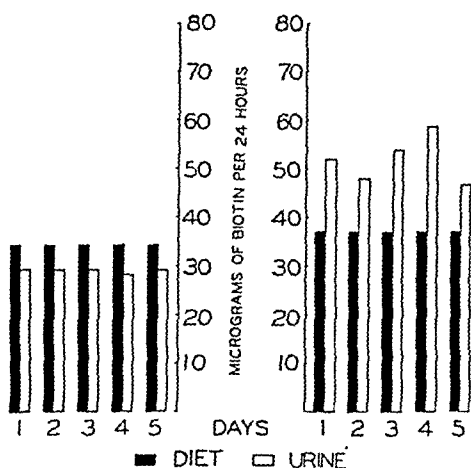


FIG. 5.—The relationship between the amounts of biotin in the diet and the urine of 2 subjects on constant diets.

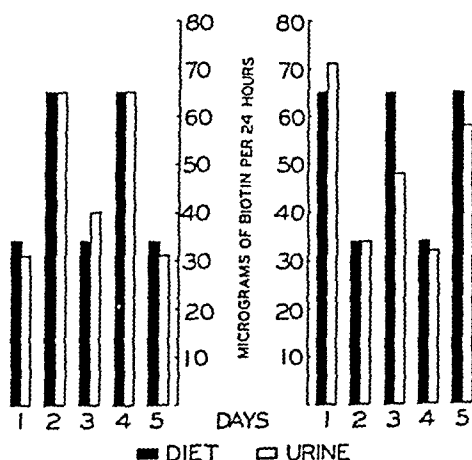


FIG. 6.—The relationship between the amounts of biotin in the diet and the urine of 2 subjects who ate diets of 35 and 65 micrograms of biotin on alternate days.

Discussion. The biotin contents of the diets used in this study probably indicate the usual range of biotin intake by normal men and women. Amounts varying from 30 to 65 micrograms a day appear exceedingly small when they are compared with the amounts of other members of the vitamin B complex in ordinary diets. The daily human consumption of the latter is often expressed in milli-

TABLE 3.—BIOTIN EXCHANGE IN THE SEVERAL METABOLISM PERIODS

Subject and number of metabolism period	Daily biotin intake in micrograms	Daily biotin output in micrograms			
		Total	Stool	Urine	
Diet Number 2					
C. Period 1	{ 34			29	
	{ 34			29	
	{ 34			29	
	{ 34			28	
	{ 34			29	
	{ —			—	
	{ 34 .	116	87	29	Average
B. Period 1	33		86		Average
L. Period 1	30		99		Average
Diet Number 3					
B. Period 3	{ 34			73	
	{ 34			53	
	{ 34			44	
	{ 34			50	
	{ 34			48	
	{ —			—	
	{ 34	217	163	54	Average
B. Period 4	{ 37			52	
	{ 37			48	
	{ 37			54	
	{ 37			59	
	{ 37			47	
	{ —			—	
	{ 37	243	191	52	Average
Diet Numbers 4 and 5					
C. Period 4	{ 34			31	
	{ 65			65	
	{ 34			40	
	{ 65			65	
	{ 34			31	
	{ —			—	
	{ 46	128	82	46	Average
C. Period 5	{ 65			71	
	{ 34			34	
	{ 65			48	
	{ 34			32	
	{ 65			58	
	{ —			—	
	{ 53	157	108	49	Average
C. Period 6	{ 62			60	
	{ 35			29	
	{ 62			65	
	{ 35			34	
	{ 62			76	
	{ —			—	
	{ 51	151	98	53	Average
W. Period 1	{ 32			37	
	{ 54			59	
	{ 32			42	
	{ 54			77	
	{ 32			47	
	{ 54			65	
	{ 32			48	
	{ —			—	
	{ 41	181	127	54	Average

grams. This relatively small biotin intake by man, however, corresponds to a similar small biotin requirement of other biologic species. For example, optimal growth of yeast occurs when biotin is present in a concentration of only .0001 micrograms per cc., while thiamine must be present in a concentration of .04 micrograms per cc. to produce optimal yeast growth.²³ The biotin requirement of animals is also very small. Hegsted, Mills, Briggs, Elvehjem, and Hart¹⁶ found that chicks require only 7 to 10 micrograms of biotin per 100 gm. of ration, a value surprisingly similar to that of our human diets. Our diets contain 2 to 4 micrograms of biotin per 100 gm. of wet ration, or from 10 to 16 micrograms of biotin per 100 gm. of dried diet.

The biotin content of the diet loses some of its importance because of the synthesis of biotin in the human intestinal tract. A number of bacteria, including *E. coli*, have been shown by Landy and Dicken¹⁸ to synthesize biotin during growth in artificial media, and they appear to form more of it than they use. Burk³ found his rats were excreting more biotin in their stools than he was feeding them. The high biotin content of the stools of our subjects thus did not come as a complete surprise. This colonic source of biotin may explain why a subject can put out more biotin in his urine than is taken in his diet, and why we found a relatively normal biotin excretion by fasting human subjects and by those who took egg white for short periods. Such findings suggest that the quantity of biotin provided from this source is adequate for the needs of man, and there is thus reason to doubt that human subjects require any biotin in their food or can be made deficient by a lack of it.

Since human subjects receive biotin from 2 sources, the significance of biotin in the urine becomes doubly complex. There is clear evidence that biotin from both sources appears in the urine. In the case of food biotin, this is shown by the striking daily variation of urinary biotin which occurred when subjects ate diets of high and low biotin content on alternate days. In the case of fecal biotin, by the continued biotin excretion which accompanies starvation and by the fact that the urine often contains more biotin than the diet. Apparently in man there is a relatively constant level of biotin excretion in the urine based on biotin synthesis by colonic bacteria, and superimposed on this, sudden variations occur due to changes in biotin content of the diet.

If this interpretation is correct, there is still no reason to doubt that the biotin content of the urine will become significantly diminished when the supply of the vitamin to the individual is greatly reduced. To produce the reduction, however, it is necessary to eliminate the supply from bacterial synthesis as well as the supply from the food. This apparently can be accomplished with diets of high egg white or avidin content. Recently Sydenstricker, Singal, Briggs, De Vaughn, and Isbell²¹ have reported levels of 3.5 to 7.3

micrograms of biotin in the urine of human subjects whom they believed to be clinically deficient. These are significantly lower than any values we have found. There is also evidence, which is presented in the following part of this paper, to show that qualitative differences of the biotin content of the urine exist, and that the value of one of the biotin-like materials found in the urine may be as significant as the total biotin level.

Conclusions. (Part II). A small group of hospital patients have been kept on diets of known biotin content and the excretion of the vitamin in their urines and feces has been studied. The following conclusions have been drawn:

1. Diets of average normal composition contained from 30 to 40 micrograms of biotin a day, which increased to 65 micrograms when liver was included.

2. On a daily biotin intake of constant value, the biotin excretion in the urine was constant for each subject. The average daily figures for the different subjects, however, varied quite widely.

3. When diets of 35 and 65 micrograms of biotin were taken on alternate days, the urine showed corresponding daily fluctuations.

4. The average daily biotin content of the feces greatly exceeded the biotin content of the diets. There seemed to be some correlation between the biotin content of the feces and the content of the urine. There was no correlation between the biotin content of the feces and the content of the diets used.

5. The total biotin output in the urine and the feces was 3 to 6 times as great as the intake in the diet.

PART III. THE EXCRETION OF TWO BIOTIN-LIKE SUBSTANCES IN URINE

The previous parts of this series report some observations on the metabolism of biotin in man, made by determining the amounts of this vitamin in diets, feces, and urine specimens. The analyses were made by a yeast growth method, and since this lacks certain desirable specific characteristics, we did many experiments throughout the work to test the properties of the material. These experiments have shown that the material in our specimens which gives the yeast growth response characteristic of biotin, can be divided by the avidin reaction into two parts, and there are thus two substances with biotin-like properties. A study of these substances is the basis of this part of our report.

Method of Analysis. The measurement of biotin was described in detail in Part I. A comparison is made between the potency of an unknown material in factors that stimulate yeast growth, and that of a solution of known biotin content. A medium from which practically all of the biotin has been removed is used, and after it has been uniformly inoculated with yeast culture it is added to the unknown and standard solutions, which are made up in varying dilutions in flasks. After incubation the turbidity of

all the flasks is measured colorimetrically and curves of the yeast growth caused by the known and unknown solutions are formed by plotting the dilution of the solution against the turbidity of it. As the biotin content of the standard solution in micrograms per cc. is known, the strength of the unknown solution can be calculated by determining what dilution of it causes a turbidity equal to that of some point on the standard growth curve. The point of half maximum growth on this curve has been arbitrarily selected as the place where the comparison is made.

Avidin is the protein responsible for the development of egg white injury in animals. It apparently produces this syndrome by combining with the biotin in their diets to form a compound which is not absorbed from their intestines. Eakin, Snell, and Williams (9a) have shown that it also prevents yeast from utilizing the biotin for growth in pure and crude solutions. Its properties have been described by these authors (9) and by Woolley (24), and its combination with biotin appears to be a specific one. Its crystalline preparation was recently described (20).

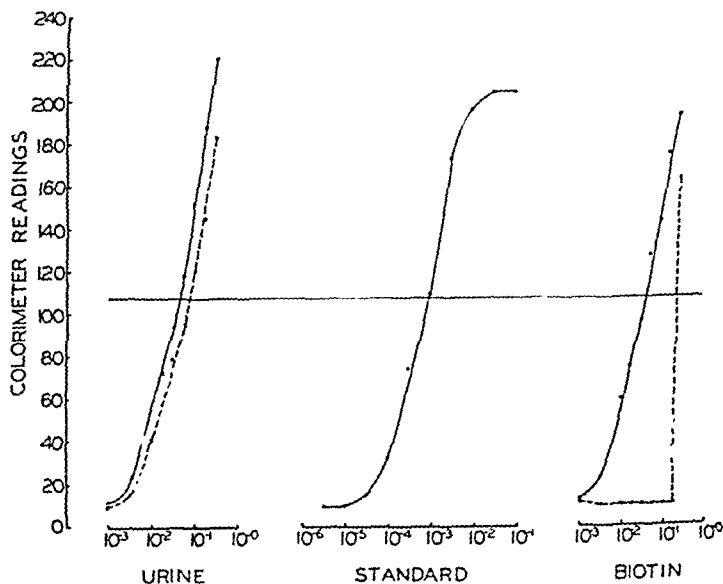


FIG. 7.—The difference between the effects of avidin on the growth factors in urine and in a biotin solution of corresponding strength. The untreated urine and biotin solutions are indicated by solid lines; the avidin treated, by interrupted lines. The growth curves are formed by plotting the dilution of the solution as the abscissa and the turbidity (colorimeter reading) as the ordinate. The standard solution contained 1 microgram of biotin per cc.

When it was found that the urine contained a material which would stimulate yeast growth on biotin-free media, attempts were made to inactivate it with avidin. A number of different urines were tested after quantities of avidin had been added that exceeded many times that needed to prevent completely the growth activity of a corresponding amount of biotin in aqueous solution. In other experiments a constant amount of avidin was added to each flask which made up the growth curve, and thus the ratio of biotin to avidin changed progressively throughout the series. When either procedure was used the avidin caused only a partial inhibition of the growth-stimulating material in the urine. The height of the growth curve was lowered and the curve was changed to a position which corre-

sponded to that of a solution of lower biotin content. In no case, however, has the growth effect of the urine been completely inhibited.

On Fig. 7 curves are shown in which the growth effects of urine and urine plus avidin are compared with solutions of pure biotin. A biotin solution was selected which gave a growth effect identical to that of the urine used. One cc. of the same avidin solution was added to all the flasks both of the biotin and the urine series. The difference between the effects of the avidin on the biotin and on the urine can be seen by comparing these curves. The avidin has completely inhibited the growth in all flasks containing $.18 \times 10^{-1}$ micrograms of biotin, or less, and the curve falls abruptly at this point. It partly inhibited the growth in the one flask containing more biotin than this. The growth in all of them, however, was inhibited to a similar degree so that a new growth curve was formed. This falls parallel to the curve for the urine without added avidin. The growth effect of the material in urine not inhibited by the avidin can be calculated, in terms of biotin activity, from the position of this new curve.

By testing a urine sample with and without avidin in this way, values are obtained for: a, all of the biotin-like growth material in urine; and, b, the amount of biotin-like material in urine which will not combine with avidin. The difference between these two values represents the amount of material in the urine that did combine with the avidin. This latter material is probably biotin.

In urine the amounts of biotin and of the biotin-like material which fails to combine with avidin are easy to measure, because both of them are present in relatively large amounts. In suspensions of diets, stools, and other biologic materials there is only a little of the non-combinable material, and the strongest possible suspensions must be tested to find it. These suspensions are colored, because they have been hydrolysed with H_2SO_4 to liberate the biotin, and a color correction must be made. We have found it practical to minimize this color correction by incubating the yeast 20 hours, instead of the usual 16 hours, so that the contents of the flasks are more turbid.

Properties of the Non-avidin Combining Growth Material. It was at first thought that the failure of avidin to inactivate all of the biotin in urine might be due to the presence of some interfering substance, most likely urea. Pure biotin was therefore added to a urea solution, which corresponded in strength to the urea in one of our urine samples. No interfering effect of the urea occurred and the biotin was completely inactivated by avidin. In other experiments pure biotin was added to urine specimens and it was found that avidin completely inactivated it without changing the amount of the other growth substance present. When urine was diluted, the same percentage of non-avidin combining growth substance always remained regardless of the degree of dilution. No evidence was thus found that anything in the urine prevented the avidin-biotin combination.

A few tests were carried out to see if the two growth substances in urine could be distinguished by any other reaction than the avidin test. It had been previously shown that HCl and H_2SO_4 hydrolysis, with concentrations of acid which do not destroy biotin, does not alter the total amount of growth substance in the urine measured by this test. Woolley²⁴ has shown that avidin is relatively stable to changes of temperature and pH. We adjusted urine samples to a

pH range of from 1 to 12 and added to them avidin solutions of corresponding pH. The amounts of biotin and non-combinable biotin-like substance in the urine were the same irrespective of the pH at which they were mixed. When urines adjusted to the same pH range were autoclaved, some of the non-combinable material changed to combinable material in the neutral range. This observation was originally made by Burk.³ Attempts to destroy biotin in urine with bromine and H_2O_2 have not been satisfactory.

A few experiments have been made to see if other substances which affect growth would alter the growth activity of the material in urine. In the presence of avidin the amount of non-combinable biotin in urine was not altered by adding folic acid, or other pure vitamins to it. Solutions of liver extract and yeast extract did increase the amount of non-combinable material under the same conditions.

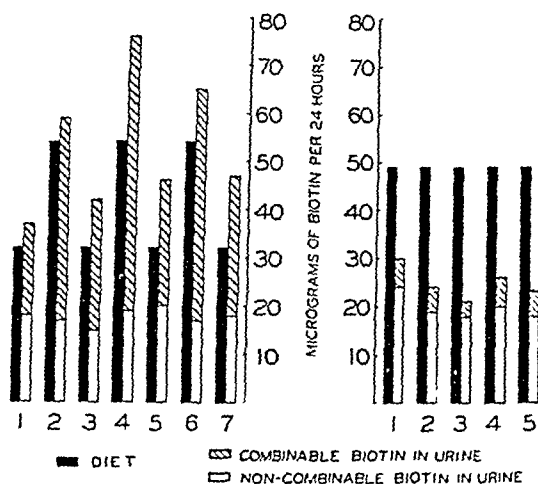


FIG. 8.—Excretion of biotin and non-avidin combining growth material in the urine. *Left*: Subject who consumed 35 and 55 micrograms on alternate days for 7 days. *Right*: Subject who consumed 47 micrograms of biotin and large amounts of egg white every day for 5 days.

Excretion of the Non-avidin Combining Growth Substance. Not only all of the human urines studied, but the urines of dogs, rabbits, and rats have been found to contain this new biotin-like growth factor. Urine is the most plentiful source of it we have found, but we do not know why it appears in the urine in such large amounts. The diets and stool specimens of patients on whom we did biotin balance studies contained so much less of it than their urine, that it could not have been absorbed from their intestines. A few experiments have been made to see what factors do alter its excretion.

The urines of 2 subjects who were eating diets containing 35 and 55 micrograms of biotin on alternate days were examined. The amount of biotin in the urine varied directly with the amount in the food. The excretion of non-avidin combining material, however,

remained quite constant. To 2 other subjects test doses of 150 micrograms of biotin were given during a period when they were maintained on diets of constant biotin content. This dose caused a flooding of the urine with biotin, but did not alter the excretion of the non-combinable material.

In another series of experiments an attempt was made to reduce the intake of biotin by giving avidin or egg white alone and with sulfanilylguanidine or succinyl-sulfathiazole. In some of the human subjects the excretion of biotin in the urine was decreased by these procedures, but it did not disappear completely. The excretion of the non-combinable biotin was not shown to be altered. We have not had an opportunity to study the urine of human subjects who showed signs of biotin deficiency, but two rats that were made biotin-deficient by avidin feeding, excreted no combinable biotin in their urine. Unfortunately, they were not studied when they consumed normal diets, so that we do not know whether or not their non-combinable biotin excretion had been changed.

The results of two typical experiments on human subjects are shown in Fig. 8.

Discussion. Of the various procedures used to identify biotin, the stimulation of yeast growth in a biotin-free medium and the inhibition of this effect by avidin are among the most specific. These tests are used to measure the amount of this vitamin in pure and crude materials, and any substance which gives both of these reactions has been considered to be biotin or some closely related compound.

Our results seem to show clearly that there is something in crude biologic materials, which gives the biotin effect on yeast growth in the presence of avidin. We have not been able to distinguish it from biotin by any other reaction, and we do not think it is any other known vitamin. The most striking thing about it, however, is that urine contains large amounts of it, though only small amounts are absorbed from the intestine. This suggests that it is formed in the animal body and one is tempted to believe that it is a product of biotin metabolism. Metabolic products of other vitamins, some with altered biologic properties, are known to appear in the urine.

Procedures intended to alter the metabolism of biotin in the body have so far failed to change the excretion of the non-combinable biotin-like substance in the urine. It seems clear that moderate variations in biotin intake and doses of biotin which greatly exceed that amount normally consumed do not alter the excretion of the non-combinable material. It is not yet clear, however, that its excretion is unchanged during periods of biotin starvation. We have not had an opportunity to make proper quantitative measurements under such conditions. The biotin absorption did not appear to be completely prevented in any of our human subjects, and the rats which appeared to be absorbing no biotin were not studied under other conditions.

While it thus appears that two substances which give the yeast growth effect of biotin can be distinguished, it is not clear how these substances are related. For this reason we have used the term biotin for the mixture of these materials in Parts I and II of this paper. In Part III, however, we have designated the materials as true biotin and non-combinable biotin for convenience, though we realize that their exact identity is not established and that the non-combinable biotin may not be a single compound. In future studies of biotin metabolism it seems important to use avidin to separate these two materials. We have done this in enough instances to form some idea of what the new procedure will show and how it will affect the results already reported.

In Part I it is stated that normal subjects excreted from 14 to 111 micrograms of biotin per 24 hours, depending on the nature of the diet. These values can be broken down into those for true biotin and non-combinable biotin. In instances where this was done the correlation between biotin intake and output was shown to be due to the fact that the daily output of non-combinable biotin is constant and uninfluenced by diet, whereas the value for true biotin fluctuates with the amount in the diet and thus provides the best index of biotin absorbed. Under those conditions where the urinary biotin values were low, the breakdown of the figures revealed that the non-combinable material accounted for such a large percentage that small variations in the excretion of true biotin were masked. When more such cases and patients with various diseases are studied with the avidin technique significant differences in biotin excretion may be found which did not show up before.

In Part II of this paper, in which the results of biotin balance studies are reported, the values for diets and stools represent true biotin, for we have not found significant amounts of non-combinable biotin in either of these. The biotin values for the urine will have to be divided, but this division does not alter the fact that the biotin in the urine and feces still exceeds by many times that present in the food, so that an important synthesis of biotin by the intestinal bacteria remains established.

While it would appear that the application of the avidin technique will amplify some of the work reported in Parts I and II of this series, we feel that more should be learned about non-combinable biotin before this is undertaken. Much remains to be known about its properties and physiology. At the same time we feel that the information already gained should be reported, as it may be helpful to other workers in the field. The present report is thus submitted with the realization that it will probably undergo some amplification and possibly some revision.

Conclusions.* (Part III). 1. The material in urine which gives the biotin test by the yeast growth assay can be separated into an avidin-combining and non-avidin-combining fraction.

* For Conclusions of Part I, see page 863; of Part II, page 869

2. Both of these fractions have been found in all human urines tested and in the urines of the dog, rabbit, and rat.

3. The avidin-combining fraction is probably biotin, and its excretion in the urine varies with the amount of biotin in the diet. Small amounts of it were excreted by patients taking diets containing large amounts of egg white. None of it was excreted in the urines of two biotin deficient rats.

4. The non-avidin-combining fraction has been found in all urine tested. The quantity in the urine was not changed by altering the biotin content of the food or by oral doses of biotin. Only minute amounts of the non-avidin-combining biotin were found in diets and stool specimens.

The author gratefully acknowledges the many suggestions and criticisms made by Dr. Vincent du Vigneaud and other members of the Department of Biochemistry of the Cornell University Medical College and the coöperation of Dr. C. P. Rhoads and his associates at Memorial Hospital, who furnished us with specimens from patients. The technical assistance of the Misses Margaret Whittemore, Betty Prescott, and Annette Pisanelli is also gratefully acknowledged.

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THE EFFECT OF VARIOUS STEROIDS IN INTACT MALE RATS

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IN previous communications¹ we described the effect of various steroids in male rats in which the gonad was either removed or damaged by estradiol treatment. These investigations revealed that certain steroids produce a more pronounced enlargement of the male accessory sex organs (so-called "androgenic" or "testoid" effect) in the presence of testicular tissue than in its absence. It was found that this activating effect of the testis is evident even if the Leydig cells have undergone complete involution as a result of estradiol overdosage. Such compounds as progesterone and pregnenolone, which fail to stimulate the seminal vesicles of the castrate rat, even in doses as high as 10 mg. per day, proved very effective in causing hypertrophy of the seminal vesicles in rats whose Leydig cells had completely involuted as a result of chronic estradiol treatment. It appeared noteworthy, however, that these same compounds (pregnenolone and progesterone) prevented the usual destruction of the seminiferous epithelium normally caused by estradiol administration. The question arose: can certain steroids stimulate the male accessory sex organs indirectly through a gonadotropic action which is mediated by the seminiferous epithelium?

It has been shown that many, if not all, hormonally active steroids cause atrophy of the Leydig cells if administered in sufficiently high doses to the rat.^{7,9} This atrophy may be accompanied by involution of the seminiferous epithelium as in the case of treatment with folliculoid compounds (*e. g.*, estradiol) or high doses of desoxycorticosterone acetate. On the other hand, progesterone produces Leydig cell atrophy without tubular damage.⁹ Testosterone proved to have a peculiar action inasmuch as in comparatively small doses it causes Leydig cell atrophy and a pronounced decrease in testis weight due to involution of the seminiferous tubules, while in high doses the tubules remain intact although the Leydig cell atrophy is even more pronounced.⁵ These facts may perhaps be explained by assuming that testosterone inhibits hypophyseal gonadotropic hormone production both at low and at high dose levels and hence tends to cause involution of both the interstitial cells and the tubular elements. At high dosages, however, the direct spermatogenic effect of testosterone prevails. Therefore the spermatogenic epithelium remains intact, while the Leydig cells, which are not directly stimulated by this compound, undergo atrophy. The fact that the spermatogenic action of testosterone is direct and not

mediated by the pituitary has clearly been proven since testosterone maintains spermatogenesis even in the hypophysectomized rat.^{3,4,5}

The experiments to be reported in this communication represent a study of the morphogenetic effects of various steroids in the intact male rat. They were designed in order to obtain further evidence concerning the changes induced in the gonad and accessory glands as well as in some other organs by a variety of steroids administered at different dose levels. We believe that these experiments clearly demonstrate that the production of Leydig cell atrophy is a common action of all the hormonally active steroids examined but is shared by none of the hormonally inactive compounds of this series. Our experiments also supply data concerning the action of the steroids on numerous other organs.

Experimental. In our first experimental series 12 groups each, consisting of 6 male rats, were injected with 12 different steroids. The 13th group acted as not injected controls. In all the injected groups the steroids were administered in 2 daily subcutaneous injections of 0.1 cc. of peanut oil each containing 0.5 mg. of the steroid to be examined. The latter was present in the oil as a fine crystalline suspension. Treatment was continued for 14 days, the animals being killed on the 15th day and at which time their organs were dissected and weighed after fixation in "Susa" solution.

Common and chemical names	Melting pt. °C.
1. Acetoxypregnenolone (17-ethyl- Δ^5 -androstene-3(β), 21-diol-20-one-21 acetate)	183-184
2. Pregnenolone (17-ethyl- Δ^5 -androstene-3(β)-ol-20-one)	186 (185-187)
3. Androstenediol (Δ^5 -androstene-3(β)-17(α)-diol)	182-183 (182-183)
4. Testosterone (Δ^4 -androstene-3-one-17(α)-ol)	154 (154.5)
5. Cholesterol (17-iso-octyl- Δ^5 -androstene-3(β)-ol)	149 (150)
6. Ethinyl testosterone (17-ethinyl- Δ^4 -androstene-3-one-17-ol)	265-268 (270-272)
7. Pregnanedione (17-ethyl-etiocolane-3,20-dione)	121 (120)
8. Pregnanediol (17-ethyl-etiocolane-3(α), 20(α)-diol)	237 (237-239)
9. Methyl testosterone (17-methyl- Δ^4 -androstene-3-one-17(α)-ol)	153 (163-164)
10. Dehydro-iso-androsterone (Δ^5 -androstene-3(β)-ol-17-one)	137 (144-146)
11. Progesterone (17-ethyl- Δ^4 -androstene-3,20-dione)	128 (128)
12. Desoxycorticosterone Acetate (17-ethyl- Δ^4 -androstene-3,20-dione-21-ol-acetate)	152 (158-160)
13. (Table 2) Androsterone (androstane-3(α)-ol-17-one)	177-178

Table 1 summarizes our findings. Both the full chemical name (in italics) and the common name are likewise mentioned here, but only the common name given in the tables: The melting-point of the sample we used was always determined in our laboratory and is mentioned as an indicator of the purity of our preparations. It may also help to identify compounds (especially isomerids) whose chemical structure is not as yet quite certain. The correct melting-point of the most highly purified preparations described in the literature are recorded in brackets for comparative purposes. In every case the average organ weight is given in the table, the maximum spread being indicated in brackets.

TABLE 1.—EFFECT OF VARIOUS STEROIDS ADMINISTERED IN

No. of group	Treatment	Dosage mg./day	Initial body wt. in g.	Final body wt. in g.	Pit. in mg.	Thyroid in mg.	Adrenal in mg.	Pancreas in mg.	Thymus in mg.	Testis in g.
1	Progesterone	1	142 (130-150)	197 (180-220)	6 (5-7)	14 (12-16)	27 (24-34)	709 (486-781)	297 (136-362)	2.572 (2.309-2.822)
2	Pregnanedione	1	141 (135-150)	203 (185-230)	7 (5-8)	14 (11-16)	28 (24-33)	679 (416-941)	288 (260-371)	2.571 (2.005-3.149)
3	Cholesterol	1	141 (130-150)	205 (180-220)	7 (6-8)	16 (13-18)	31 (24-40)	734 (592-849)	319 (230-363)	2.516 (2.227-2.780)
4	Non-injected	142 (135-155)	205 (180-230)	6 (5-9)	17 (16-18)	30 (20-38)	750 (508-935)	355 (267-425)	2.465 (2.245-2.785)
5	Acetoxypregnenolone	1	142 (130-155)	202 (170-225)	6 (5-7)	14 (10-18)	30 (24-38)	658 (414-838)	318 (235-406)	2.417 (2.167-2.730)
6	Desoxycorticosterone acetate	1	142 (135-150)	204 (180-230)	6 (6-7)	13 (11-15)	31 (26-40)	768 (594-963)	248 (174-302)	2.401 (2.133-2.730)
7	Pregnenolone	1	142 (130-155)	194 (150-210)	6 (5-7)	13 (11-14)	26 (23-29)	644 (438-823)	252 (170-349)	2.393 (1.914-2.676)
8	Androstenediol	1	141 (135-150)	198 (180-210)	6 (4-7)	14 (11-18)	27 (21-32)	805 (688-929)	288 (152-503)	2.369 (2.061-2.440)
9	Ethinyl testosterone	1	143 (135-145)	195 (185-205)	6 (6-7)	13 (9-14)	28 (25-33)	636 (461-783)	251 (183-315)	2.399 (2.035-2.635)
10	Androsterone	1	139 (135-150)	169 (164-174)	5 (3-5)	..	25 (18-30)	399 (322-543)	242 (164-359)	2.258 (2.050-2.418)
11	Dehydro-iso-androsterone	1	142 (130-150)	197 (180-215)	7 (5-8)	16 (13-18)	29 (26-33)	787 (516-912)	230 (165-285)	2.248 (2.004-2.471)
12	Methyl testosterone	1	141 (130-165)	211 (185-240)	7 (5-9)	13 (11-15)	32 (25-41)	797 (604-1,032)	277 (200-379)	2.116 (1.455-2.692)
13	Testosterone	1	141 (130-165)	192 (165-225)	5 (5-6)	13 (11-18)	27 (23-30)	832 (724-1,021)	233 (168-331)	1.708 (1.569-1.837)

TABLE 2.—EFFECT OF VARIOUS STEROIDS ADMINISTERED IN

No. of group	Treatment	Dosage in mg./day	Initial body wt.	Final body wt.	Pit. in mg.	Thyroid in mg.	Adrenal in mg.	Pancreas in mg.	Thymus in mg.	Testis in g.
1	Acetoxypregnenolone	10	143 (130-150)	201 (195-216)	6 (5 2-6 4)	16 (13-20)	28 (22-32)	624 (356-711)	279 (182-441)	2.419 (1.915-2.849)
2	Pregnenolone	10	143 (130-150)	200 (190-210)	6 6 (6 2-7 0)	17 5 (16-19)	31 5 (29-35)	676 (571-840)	283 (181-355)	2.391 (2 275-2 505)
3	Androstenediol	10	143 (130-150)	183 (145-215)	6 1 (5 1-7 0)	16 (12-21)	29 (27-33)	564 (440-763)	236 (180-381)	2.341 (2 215-2 521)
4	Testosterone	10	144 (140-150)	192 (185-200)	6 2 (5 3-7 0)	16 6 (13-22)	34 6 (25-42)	635 (549-770)	117 (88-185)	2.328 (2 201-2 505)
5	Cholesterol	10	143 (130-150)	196 (170-215)	6 8 (6 4-7 2)	17 (16-18)	33 (30-36)	644 (547-755)	270 (181-358)	2.324 (2 115-2 440)
6	Ethinyl testosterone	10	142 (130-150)	183 (160-202)	6 (5 1-6 9)	17 (15-20)	31 (26-35)	605 (435-814)	249 (165-345)	2.120 (1 505-2 644)
7	Pregnanedione	10	143 (135-150)	189 (170-202)	6 2 (4 9-7 5)	15 (10-20)	33 5 (28-34)	623 (240-872)	249 (168-398)	2.114 (1 505-2 644)
8	Pregnanediol	10	143 (130-150)	179 (145-197)	6 3 (5 1-7 1)	14 (11-18)	39 (27-35)	617 (490-810)	181 (98-271)	2.064 (1 505-2 644)
9	Methyl testosterone	10	143 (130-150)	176 (167-196)	5 (4 7-5 4)	15 (13-19)	33 (31-35)	638 (505-772)	76 (36-121)	2.025 (1 505-2 545)
10	Dehydro-iso-androsterone	10	143 (130-150)	178 (140-190)	6 4 (6 0-6 8)	17 (15-20)	33 (28-40)	613 (394-801)	129 (83-161)	2.025 (1 505-2 545)
11	Progesterone	10	143 (135-150)	175 (145-205)	5 9 (5 4-6 4)	16 (14-19)	31 (29-35)	612 (533-663)	253 (158-455)	2.013 (1 205-2 605)
12	Desoxycorticosterone acetate	10	143 (130-150)	169 (160-175)	5 3 (4 8-6 0)	15 (12-20)	19 (15-21)	524 (491-725)	147 (114-178)	1.722 (1 225-2 140)

COMPARATIVELY LOW DOSAGES ON WEIGHTS OF VARIOUS ORGANS

Seminal vesicles in mg.	Ventral prostate in mg.	Middle prostate in mg.	Epididymis in mg.	Preputial gland in mg.	Coag. gland in mg.	Cowper gland in mg.	Liver in g.	Spleen in g.	Kidney in g.	Heart in mg.
177 (118-217)	144 (127-156)	94 (85-101)	451 (360-566)	47 (36-62)	39 (35-41)	20 (18-24)	8.796 (7.171-10.319)	1.587 (1.215-2.075)	1.709 (1.442-2.118)	723 (600-890)
308 (169-478)	156 (120-200)	124 (87-176)	492 (400-586)	57 (38-85)	60 (33-99)	26 (17-32)	10.310 (9.585-10.720)	1.546 (0.964-1.977)	1.805 (1.682-1.972)	761 (670-978)
268 (230-372)	152 (114-212)	103 (67-142)	449 (352-581)	63 (35-79)	56 (46-81)	26 (20-37)	10.054 (8.496-11.242)	1.670 (1.204-2.245)	1.668 (1.485-1.860)	766 (639-907)
319 (253-426)	170 (136-196)	110 (92-120)	497 (428-558)	58 (40-88)	61 (39-74)	33 (28-43)	10.007 (8.068-12.298)	1.504 (1.219-2.094)	1.818 (1.442-2.185)	807 (715-999)
241 (137-368)	149 (88-190)	114 (67-147)	461 (305-596)	51 (31-71)	49 (24-73)	30 (16-50)	10.148 (7.351-12.043)	1.269 (0.435-2.304)	1.821 (1.352-2.146)	772 (517-886)
285 (192-439)	149 (107-203)	108 (84-150)	495 (353-608)	58 (34-89)	55 (41-77)	29 (20-35)	9.583 (8.150-11.244)	1.440 (0.990-1.862)	1.815 (1.569-2.020)	768 (605-858)
334 (125-468)	157 (80-200)	130 (75-171)	481 (345-590)	46 (38-56)	61 (28-88)	29 (19-36)	9.586 (7.702-11.300)	1.648 (1.181-2.300)	1.550 (1.273-1.824)	667 (478-765)
247 (175-338)	153 (112-176)	113 (80-150)	428 (371-480)	61 (38-79)	49 (36-65)	25 (18-29)	9.973 (9.007-12.454)	1.285 (0.924-1.803)	1.679 (1.482-2.050)	714 (654-846)
300 (171-479)	164 (130-201)	116 (82-165)	484 (302-750)	70 (48-107)	62 (43-96)	30 (20-42)	9.223 (8.042-10.028)	1.307 (0.781-1.605)	1.595 (1.492-1.685)	748 (628-866)
176 (63-296)	186 (134-253)	151 (93-194)	511 (402-598)	49 (31-92)	42 (22-76)	19 (16-26)	8.175 (7.006-8.670)	1.034 (0.804-1.265)	1.582 (1.528-1.610)	638 (564-756)
281 (241-330)	167 (140-193)	123 (107-130)	501 (439-534)	61 (57-72)	58 (50-65)	33 (27-39)	9.535 (8.831-10.431)	1.308 (0.900-1.617)	1.573 (1.474-1.690)	697 (522-887)
386 (262-478)	190 (126-250)	145 (123-170)	466 (327-587)	79 (43-92)	76 (34-95)	43 (30-54)	11.312 (10.282-12.263)	1.748 (1.226-2.134)	1.876 (1.638-2.100)	776 (672-848)
462 (303-634)	211 (150-300)	168 (139-188)	401 (324-483)	65 (36-94)	90 (56-160)	34 (29-51)	9.693 (8.481-10.949)	1.340 (1.042-1.930)	1.642 (1.432-1.942)	718 (566-938)

COMPARATIVELY HIGH DOSAGES ON WEIGHTS OF VARIOUS ORGANS

Sem. ves. in mg.	Ventral prostate in mg.	Middle prostate in mg.	Epididymis in mg.	Prep. glands in mg.	Coag. glands in mg.	Cowper's glands in mg.	Liver in g.	Spleen in g.	Kidney in g.	Heart in mg.
305 (155-410)	197 (113-272)	143 (84-179)	570 (366-720)	70 (62-95)	69 (36-85)	30.5 (19-45)	7.213 (6.630-7.840)	1.298 (0.871-1.655)	1.564 (1.368-1.775)	879 (646-1100)
375 (260-576)	229 (175-298)	180 (155-238)	541 (430-655)	107 (77-152)	80 (53-131)	49 (35-64)	7.366 (6.374-9.071)	1.206 (0.850-1.718)	1.524 (1.365-1.734)	855 (715-1070)
253 (133-361)	192 (143-239)	122 (111-132)	514 (433-563)	103 (80-135)	57 (43-74)	34 (31-37)	6.558 (5.242-7.545)	1.272 (0.580-1.780)	1.331 (1.170-1.434)	831 (738-934)
1179 (725-1510)	380 (272-465)	298 (271-350)	563 (430-671)	158 (82-286)	207 (150-245)	73 (68-81)	6.185 (5.789-6.490)	0.910 (0.660-1.234)	1.511 (1.350-1.714)	798 (733-970)
306 (250-342)	189 (163-220)	158 (114-211)	535 (404-680)	82 (70-98)	54 (40-70)	33 (29-49)	6.527 (5.907-6.960)	1.764 (1.129-2.450)	1.378 (1.210-1.503)	825 (777-910)
293 (196-341)	178 (140-246)	131 (111-144)	482 (304-540)	70 (52-90)	66 (54-92)	38 (29-45)	6.367 (4.830-7.583)	1.263 (0.830-1.763)	1.290 (1.076-1.545)	731 (637-871)
272 (152-421)	154 (83-210)	113 (76-143)	439 (342-479)	66 (50-76)	63 (28-120)	34 (18-46)	8.211 (7.265-9.998)	1.607 (1.155-2.102)	1.429 (1.318-1.535)	787 (712-840)
269 (112-447)	166 (94-223)	114 (74-157)	464 (343-600)	67 (43-89)	62 (34-95)	36 (22-50)	6.439 (4.893-7.280)	1.394 (0.790-2.231)	1.360 (1.261-1.445)	717 (620-845)
1188 (905-1424)	414 (330-515)	320 (214-420)	694 (432-745)	103 (65-129)	195 (142-244)	69 (61-86)	5.729 (4.769-6.259)	1.099 (0.917-1.324)	1.381 (1.140-1.645)	696 (514-912)
768 (507-976)	339 (208-414)	281 (236-320)	556 (494-695)	150 (75-206)	138 (68-175)	67 (54-76)	7.603 (6.110-8.693)	1.141 (0.655-1.498)	1.488 (1.215-1.831)	805 (670-925)
185 (70-325)	175 (122-310)	122 (85-168)	439 (345-608)	65 (45-85)	46 (25-99)	32 (24-55)	6.803 (5.896-7.640)	1.333 (1.035-1.850)	1.312 (1.213-1.412)	795 (621-953)
74 (46-96)	96 (61-128)	67 (49-82)	366 (251-516)	48 (34-64)	20 (12-27)	20 (14-27)	6.721 (6.433-7.066)	1.517 (0.704-2.201)	1.466 (1.329-1.596)	693 (596-775)

It will be noted that in the table the compounds are arranged according to decreasing average testis weight. The most striking fact which emerges from a perusal of the table is that in these comparatively low doses only testosterone, and to a lesser degree methyl testosterone, cause a pronounced decrease in testis weight. The seminal vesicles, on the other hand, are most markedly stimulated by these 2 compounds.

A second series of experiments is summarized in Table 2. It was performed in exactly the same manner as the first series except that the steroids were administered in bi-daily doses of 5 mg., each dose being given as a suspension in 0.1 cc. of peanut oil.

It will be noted that in Table 2 the steroids are also enumerated according to decreasing testis size, but at this high dose level desoxycorticosterone acetate is most active in causing testis atrophy. This we believe is due to the fact that this steroid—unlike testosterone—is entirely devoid of any direct spermatogenic action. Thus its ability to produce gonad atrophy, by inhibiting hypophyseal incrition, becomes more and more evident as the dose increases. By comparing the average weights of the testes in the various treated groups with the non-injected controls (Group 4 in Table 1) it will be noted that none of these compounds succeeded in enlarging the testes above their normal weight. However, it may be said in confirmation of our earlier findings, quoted above, that high doses of testosterone do not cause such marked testis involution as may be obtained by comparatively small doses. It will also be observed that the seminal vesicles are most markedly stimulated by testosterone and methyl testosterone, then follows dehydro-*iso*-androstosterone. This is in agreement with the results of similarly conducted experiments in castrate rats.⁸ On the other hand, desoxycorticosterone caused very pronounced involution of all the male accessory sex organs. It will be noted that in the case of most other steroids the average size of the seminal vesicles, though rather variable, is not very different from that of the not injected controls. This is probably due to the fact that in most cases the decrease in endogenous testis hormone production, which results from the Leydig cell atrophy produced, is approximately compensated for by the testoid action of the compounds in question.

The thymus underwent particularly pronounced atrophy following treatment with the 3 most active testoid compounds (Cpds. 4, 9, 10) as well as following injection with desoxycorticosterone acetate. It will be noted that the other steroids did not cause any significant loss in thymus weight in this experimental series of comparatively short duration. It should be emphasized, however, that in the case of more chronic treatment all hormonally active steroids so far examined cause some thymus involution.⁷ The comparative irresponsiveness of the thymus in such short-term experiments is especially noteworthy as it represents a good example of

the difference in the speed with which the steroids induce changes in different organs. The sex organs and the adrenals (the latter undergo involution under the influence of corticoids and enlargement after treatment with folliculoids) respond very quickly, while the thymus is more sluggish and the other organs mentioned in our tables show almost no change within 2 weeks although numerous experiments performed in this as well as in other laboratories⁷ show that after 3 or 4 weeks of treatment even much smaller doses of testoids cause enlargement of the kidney, spleen, heart, liver and pancreas as well as an increase in total body weight.

Histologic examination of the testes of all animals in both the above-mentioned experimental series revealed that, irrespective of the specific types of their main activity, all hormonally active compounds used in these experiments caused some degree of Leydig cell involution. This was particularly pronounced in the 10 mg. per day series and was roughly proportional to the dose used. The average degree of atrophy in each group is indicated in Table 3 by a scale in which "0" indicates the normal condition and "++++" the maximum degree of Leydig cell atrophy. In this table the compounds are enumerated according to increasing Leydig cell size.

Testosterone and methyl testosterone proved to be by far the most active compounds in this series as far as production of Leydig cell atrophy is concerned. It must be kept in mind, however, that the folliculoid estrane derivatives (not represented in this experiment) are even more potent in this respect. All other hormonally active steroids were likewise endowed with varying degrees of the anti-Leydig cell effect, while the two groups receiving hormonally inactive steroids (cholesterol and pregnanediol) possessed Leydig cells identical with those of the not injected controls. This clearly indicates that the daily handling of the animals and the injection of oily solutions of steroid compounds, as practiced in these experiments, does not suffice to damage the Leydig cells. The observations confirm the generalization previously made on the basis of a smaller group of steroid compounds⁷ namely that all hormonally active steroids exhibit folliculoid actions.

It will be recalled that some pharmacologic properties of folliculoid estrane derivatives are inhibited by simultaneous treatment with steroids belonging to other pharmacologic groups. Thus the vaginal cornification, the involution of the seminal epithelium and the enlargement of the adrenal cortex caused by estradiol may all be inhibited by simultaneous administration of such compounds as progesterone or testosterone. Desoxycorticosterone inhibits the vaginal cornification and the adrenal enlargement but not the involution of the testicular tubules. Other pharmacologic actions of the estranes are not inhibitable by simultaneous treatment with steroids belonging to different pharmacologic groups. The anti-Leydig cell effect, the anti-castration cell effect, as well as the pro-

duction of thymus atrophy belong to this category of the "non-inhibitable" folliculoid actions. It is evident that even if the above-mentioned theory is correct and all hormonally active steroids are endowed with a certain degree of folliculoid potency, those folliculoid effects which are inhibited by other steroid hormones will not necessarily be manifest in every compound since other hormonal actions of the same steroid molecule may mask these inhibitable folliculoid effects. The production of Leydig cell atrophy, on the other hand, which is a non-inhibitable effect, should be demonstrable according to the theory in the case of every hormonally active steroid irrespective of the specific nature of its other hormonal actions. The present experimental series clearly proves this to be the case. It also proves that although the 2 most active testoids were most potent among the compounds examined with regard to their ability to produce Leydig cell involution, this action is not a function of their testoid potency since desoxycorticosterone, which possesses no testoid effect is more active than androstenediol although the latter is definitely testoid. Considering that in the case of folliculoids (estradiol, estrone, estriol) a few gamma per day suffice to cause Leydig cell involution, it appears justified to regard this effect as subordinate to the folliculoid action. It will be noted that since the anti-Leydig cell effect is non-inhibitable it serves as a valuable aid for the estimation of the degree of folliculoid potency in testoid, luteoid, corticoid and spermatogenic steroids in which most other folliculoid actions are usually masked.

Until recently the folliculoid potency of a compound was usually estimated by a determination of the minimum dose capable of producing vaginal cornification in the spayed rodent. However, since this effect is inhibited by the other hormonal actions of many steroids, it is no indication of true folliculoid potency. Using the anti-Leydig cell effect as a gauge of the true folliculoid power of steroids, our compounds should appear in Table 3 in decreasing order of this activity. The ability of steroids to prevent the development of castration cells in the pituitary of gonadectomized male or female rats, and their ability to cause thymus involution are also good indicators of folliculoid potency since they are also non-inhibitable by other steroid hormone actions. It is gratifying to note that if the above-mentioned steroids are arranged according to decreasing activity in the latter two tests, the order is approximately the same as that given in Table 3.²

The testis atrophy caused by comparatively small doses of testosterone proved to result from the degeneration of the spermatogenic cells. This effect is not due to the "male hormone" activity of the compound since most other testoid substances are practically free of this action at any dose level, while estradiol and desoxycorticosterone acetate are very active in this respect although they are not testoid.

TABLE 3.—LEYDIG CELL ATROPHY CAUSED BY VARIOUS STEROIDS

	Dosage	
	1 mg. per day	10 mg. per day
Testosterone	+++	++++
Methyl testosterone	+++	++++
Progesterone	+	+++
Dehydro- <i>iso</i> -androsterone	+	+++
Ethinyl testosterone	+	+
Pregnenolone	0	++
Androsterone	+	not tested
Androstenediol	+	+
Desoxycorticosterone acetate	+	+
Acetoxy pregnenolone	trace	trace
Pregnanedione	0	0
Cholesterol	0	0
Not injected	0	0

Summary. The effects on organ structure of various synthetic steroids have been studied in intact male rats.

The most important result obtained from these investigations was the finding that all hormonally active steroids cause involution of the Leydig cells in the testis. This is true of compounds whose predominant hormonal action is folliculoid (estradiol), testoid (testosterone, methyl testosterone), luteoid (Progesterone), corticoid (desoxycorticosterone acetate) or spermatogenic (pregnenolone). Generally speaking, the activity decreases in the order in which the compounds are mentioned here. It is noteworthy, however, that when calculated per milligram of substance the folliculoids are very much more active in this respect than hormones belonging to any other group. This observation adds further support to the theory that actions exhibited to a particularly marked degree by folliculoids, are demonstrable—at least in traces—in all hormonally active steroids. That is to say a certain amount of folliculoid (or “estrogenic”) potency is a characteristic and an inherent property of all steroid hormones.

It is almost certain that the Leydig cell involution is not a direct effect of these steroids but secondary to their power to inhibit pituitary gonadotropic hormone secretion. Yet this indirect action is an especially valuable indicator of folliculoid potency because it belongs to those few pharmacologic properties of the folliculoids which are not inhibitable by simultaneous treatment with steroids belonging to other hormonal groups. Hence no matter what the main activity of a steroid may be, it is not likely to interfere with this particular folliculoid effect. Thus in the present experimental series the Leydig cell atrophy produced by various steroids was used for the estimation of their folliculoid potency.

The tubular damage elicited by comparatively small doses of testosterone is not due to the testoid (or androgenic) effect of this compound, since most other testoids fail to cause testis involution at any dose level.

The action of the steroids on the structural appearance of numerous other organs has also been tabulated.

The expenses of this investigation were defrayed by the Blanche E. Hutchinson Fund of McGill University. The authors are especially indebted to Dr. E. Schwenk of the Schering Corporation of Bloomfield, N. J., for supplying most of the steroids used in this work. The androsterone was kindly supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

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BOOK REVIEWS AND NOTICES

NEUROANATOMY. By FRED A. METTLER, A.M., M.D., Ph.D., Professor of Anatomy, University of Georgia School of Medicine, Augusta, Ga. Pp. 476; 337 figures, 30 in color. St. Louis: The C. V. Mosby Company, 1942. Price, \$7.50.

This newest text on neuroanatomy gives a fresh treatment of the subject. Part I treats the gross aspect of the neural system in 179 pages and 121 figures. Part II treats the microscopic aspect in 197 pages and 216 figures and is exceptionally well done. Mettler does not burden the text by quoting his authorities, although there are places where it would be desirable to know his source. A selected bibliography is given for certain sections. Most of the illustrations are original, others are redrawn and relabeled to conform to the text. This book will prove a valuable addition to the teaching texts and should be very useful as a reference book for the neuropathologists and for the physician with a special interest in the nervous system.

CASTOR OIL AND QUININE: ONCE A DOCTOR, ALWAYS A DOCTOR. By GEORGE WILSON VANDEGRIFT, M.D. Pp. 252. New York: E. P. Dutton & Co., Inc., 1942. Price, \$3.00.

In arresting contrast to the usual protective statement, the dedication of this book reads: "Every character in this book is real. If there is any similarity to fiction it is purely coincidental." This, then, is the key to the amusing biography of the "Corner Doctor," as he was known most of his life (his home and office being on the corner).

Although the book has widespread appeal for laymen and professional men alike because of its easy readability, those primarily interested in historic progress, particularly in the prodigious changes in early New York City, will find this of especial interest. The medical profession *per se* has an appeal all its own through its intimate linkage with human lives. Many books have come upon the market in the last few years concerned with the lives of the practising physician. In this day of specialization and sterile institutionalism, the books seem to assuage a hunger of those who lose touch with a patient because of "necessary paper work (case histories, laboratory reports, file records)." Such books, perhaps, have even wider appeal to the lay public, for their bewilderment at being a specimen instead of a human being is often more intense.

At any rate, this book falls worthily into the class of popular appeal. It is amusing and relaxing for an evening's entertainment. "Warm with humanity, humor and vitality, Dr. Vandegrift's biography of his father adds another strong, appealing picture to the growing gallery of American Fathers who have come back in recent years to amuse us, to entertain us, and to remind us of our rich heritage."

E. F.

BIOLOGICAL SYMPOSIA. VOL. VIII. LEVELS OF INTEGRATION IN BIOLOGICAL AND SOCIAL SYSTEMS. Edited by ROBERT REDFIELD, Professor of Anthropology; Dean of the Division of Social Sciences, University of Chicago. Pp. 240; 4 figures. Lancaster, Pa.: Jacques Cattell Press, 1942. Price, \$2.50.

The 12 papers of this symposium represent the material from one of the conferences held to celebrate the 50th anniversary of the University of Chicago. They constitute a logical sequence of studies progressing from

the lowliest unicellular organisms to the complexities of modern society, studies mostly presented by Chicago scientists. Such titles as "The Transition From the Unicellular to the Multicellular Individual" (L. H. Hyman), "The Transition From the Individual to the Social Level" (H. S. Jennings); "Basic Comparisons of Human and Insect Societies" (A. E. Emerson), "Societies of Monkeys and Apes" (C. R. Carpenter); "The Societies of Primitive Man" (A. L. Kroeber) indicate the range of subject matter and authors. While some parts will obviously appeal to biologists, others to anthropologists, and others to sociologists, the value of such present-status books, like those of the Harvard Tercentenary and the Pennsylvania Bicentenary celebrations, is self-evident.

It will be recalled that the previous volumes of this series of Biological Symposia were on The Cell; Species; Muscle; Biochemistry; and miscellaneous topics such as Temperature; Visual Mechanisms, etc.

E. K.

ORNITHOLOGISTS OF THE UNITED STATES ARMY MEDICAL CORPS. By EDGAR ERSKINE HUME, COL., M.C., U.S.A. Pp. 583; 109 illustrations. Baltimore: The Johns Hopkins Press, 1942. Price, \$5.00.

THIS interesting volume brings together for the first time the contributions to ornithology of workers of the United States Army Medical Corps. To some it will come as a surprise that army surgeons should have played a part in the development of American ornithology. That they did largely depended upon the inspiration of Prof. Spencer Fullerton Baird of the Smithsonian Institute. Through his efforts Army surgeons sent into the undeveloped West were chosen with a view to their capacity to act as scientists, in addition to the performance of their routine duties. The greater part of the book is devoted to the 19th century, when advance in ornithology was rapid. A list of ornithologists in the Army Medical Corps after the World War is appended.

The book is well organized, satisfactorily illustrated and filled with entertaining anecdotes concerning such famous ornithologists as Cassin, Heermann, Coues, Cooper and Means—names familiar to all present-day ornithologists. Many lesser lights are also treated in the 36 biographies that are included. The book is of value as a group of biographic sketches, rather for those interested in the history of the American Sciences than for contemporary ornithologists or army surgeons. It gives the less specialized reader a fascinating picture of a little known part in the cultural and scientific growth of the United States.

D. C.

EDINBURGH POST-GRADUATE LECTURES IN MEDICINE. VOL. II, 1940-41. Thirty-three contributors. Pp. 540; several figures. Edinburgh and London: Published for Honyman Gillespie Trust by Oliver & Boyd, 1942. Price, 12/6 net.

THE 33 lectures presented in this volume perform a variety of functions. They afford an up-to-date review of some of the intellectual background of medicine which has frequently grown dim in the memory of the practitioner. Lectures in which this cultural influence dominates includes: Contributions of Genetics to Medicine; The Basis of Temperament; The Significance of Fear; Inspection; Physiological Approach to Medical Problems.

The majority of the lectures present the practical aspects of selected topics. At least 17 of them deal with problems relating to surgery or to war medicine, fields in which British medical opinion is welcome. The writers

are authorities in their respective subjects and know how to use the English language.

The book will not replace textbooks and scientific articles. Incidentally, it raises the question of the relative value of collected lectures *vs.* lectures scattered in the medical journals. It will review technical knowledge and add to the perspective of medicine as postgraduate education should. Finally, the most valuable service of this volume will be to provide a few very pleasant evenings for the progressive physician. F. L.

PLASTIC SURGERY OF THE BREAST AND ABDOMINAL WALL. By MAX THOREK, M.D., LL.D., F.I.C.S., F.I.C.A., K.L.H. (France); K.C.I., C.O. St. Alex., Medal of Hon. Rep. of Venezuela; Professor of Surgery, Cook County Graduate School of Medicine; Attending Surgeon, Cook County Hospital; Surgeon-in-Chief, American Hospital of Chicago; Fellow (Honoris Causa), Surgical Society, Sofia, Bulgaria; Corr. Academician, Mexican Academy of Surgery; Fellow, National Gastroenterological Society; Corresponding Member, Société de Chirurgiens de Paris; Royal Academy of Medicine, Torino, Italy; Surgical Society, Madrid, Spain; Sociedade das Ciencias Medicas de Lisboa, Portugal; Fellow, National Academy of Medicine, Columbia, South America; Honorary Fellow, Peruvian Academy of Surgery; Honorary Fellow, Egyptian Medical Association, Cairo, Egypt. With an Introduction by RUDOLF NISSEN, M.D., F.I.C.S., and a Foreword by J. EASTMAN SHEEHAN, M.D., F.A.C.S. Pp. 446; 458 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$16.50.

THIS volume represents an exhaustive presentation of the standardized procedures on plastic surgery of breast abnormalities and reconstructive surgery of the abdominal wall augmented by the author's researches and original technique. Instructive chapters on the anatomy, physiology, pathology, embryology and racial characteristics of the breast supplement the surgical considerations. The well-trained general surgeon desiring to add this special field to his activities, as well as the specialist wishing to possess a complete reference volume dedicated to this subject exclusively, will find this book worthwhile. The surgeon is enabled to acquaint himself with the various technical details demanded by the particular case in point. The outline of surgical technique is meticulous and yet not elementary. The profusion of excellent illustrations greatly enhances the understanding of the text. The chapters devoted to the problem of breast hypertrophy are particularly valuable. Chapters on other correlated subjects such as scar and keloid formation, plastic operations following surgical removal of the breasts and diseases of the nipples are also included. L. S.

PULMONARY TUBERCULOSIS AND ITS TREATMENT. By HANS JACOB USTVEDT, M.D., First Assistant Physician to the State Hospital, Oslo, translated by A. L. JACOBS, M.R.C.P. Pp. 252; 45 figures, 11 graphs, 2 tables. London: John Bale & Staples, Ltd., 1942. Price, 25/-

THIS book is divided into 5 chapters. The 3 chapters dealing with tuberculous infection, with phthisis and with the treatment of clinical pulmonary tuberculosis are relatively long and detailed. The chapter on miliary tuberculosis is short for obvious reasons and the final chapter on prophylaxis is very brief.

Scandinavian investigators have made many noteworthy contributions in the tuberculosis field. Due to distance and to language difficulties, their work is not as well known to the American phthisiologist as it deserves to be.

Apart from the actual medical value of this book, the presentation in a compact form of the results of reported papers that were published in Norwegian, German and French as well as in English, making available the work and theories of leading Scandinavian tuberculosis specialists, is a worthwhile contribution to English medical literature. It must be pointed out that both the theories and the findings reported by Dr. Ustvedt are frequently at variance with commonly accepted theories and investigative results of tuberculosis workers in the United States. The incidence of erythema nodosum, the remarkably high incidence of clinical tuberculosis immediately following first infection, and disbelief in the importance of re-infection (or superinfection) may be cited in this regard. Accordingly, this book cannot be recommended for the beginning student of tuberculosis in the United States but it should be in the hands of every advanced student of this disease.

H. H.

INTRODUCTION TO PARASITOLOGY. By A. S. PEARSE, Professor of Zoölogy, Duke University. Pp. 357; 448 figs. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.75

As a phase of natural history, adaptations to the parasitic habit are interesting reactions of organisms to their environment, and undoubtedly study of such reactions should form part of training in Biology.

But one wonders that it should be necessary to place so much emphasis on organisms that are parasitic in man in such courses, and one is surprised that independent courses in parasitology should have become so common in college curricula. Is this the result of student demand, of efforts to prepare students for jobs in public health laboratories, or simply an easy way for zoölogy departments to provide interesting material? Why not, then offer bacteriology or histology and omit altogether any consideration of the life histories and interrelationships of the animals and plants which make up our environment? These remarks are not offered in criticism of Professor Pearse's book, which is indeed an excellent introduction and guide to the study of animal parasites. It is to be regretted, however, that the author considered emphasis of parasites of man necessary or that treatment be described. For there he is incomplete and sometimes inaccurate. The book cannot be recommended as an aid to physicians or medical students; but, they too will find in it much that will interest, as it includes a much wider field than parasitic organisms of men.

H. R.

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOCHEMISTRY AND MEDICINE. By EDWARD S. WEST, Ph.D., Professor of Biochemistry and Medicine in the University of Oregon Medical School. Pp. 368; 32 tables, many figures. New York: The Macmillan Company, 1942. Price, \$5.75.

THIS textbook, as the title implies, is planned entirely for students of Medicine and Biology. Not only has the general subject matter been chosen with this in view but examples of the various theories discussed have been selected from the field of biology. Since it is a text intended for a special group of students, many of the subjects usually covered in a textbook of Physical Chemistry have been omitted. The subject matter is discussed under the following chapter headings: Introduction, The Structure of Matter and Some Fundamental Chemical Principles, Gases and Solutions, Osmotic Pressure, Electrolytic Dissociation and the Mass Law, Acids, Bases, and Buffers, The Determination of pH, The Colloidal State and Membrane Phenomena, Oxidation and Reduction, The Velocity of

Reactions. At the end of each chapter is a set of questions and a brief list of references.

The author has succeeded in presenting a subject, which is frequently difficult for students of Medicine, in an exceedingly clear manner but in so doing, there has been no attempt to avoid the more difficult topics. Considerable space is devoted to the modern viewpoints on atomic structure, valence, radioactive and isotopic elements, acids and bases, isoelectric points of proteins, etc.

Although probably being more physics than chemistry a chapter on photometry and the fundamentals underlying the use of the photoelectric colorimeter and spectrophotometer could have been included in the opinion of the Reviewer. This suggestion is made because these instruments and methods are being so widely and commonly used in biological and clinical chemistry.

This book should be ideal as a text in a short course given to pre-medical and other students not primarily chemists. It should also find use as a supplementary text in courses in biologic chemistry. For these purposes it is highly recommended.

J. J.

RECENT ADVANCES IN MEDICINE. By G. E. BEAUMONT, M.A., D.M. (OXON), F.R.C.P., D.P.H. (LOND.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Traveling Fellow, University of Oxford; and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., F.I.C., F.R.S.E., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopaedic Hospital. Tenth Edition. Pp. 440; 45 illustrations. Philadelphia: The Blakiston Company, 1941. Price, \$5.00.

LIKE other "Recent Advances," the contents of this book belie the title in, perhaps necessarily, including much that could not be called recent. For instance, the article in cardiac arrhythmias begins with Potain and McKenzie and gives a classical description, with illustrations, of the various arrhythmias. Comparison with the ninth edition shows that the authors have not been idle. "The most important changes are as follows: The description and clinical applications of the sulphanilamide drugs have been brought up to date in Chapter I and an article on sulphathiazole included. In Chapter II the vitamin B section has been largely rewritten. The descriptions of vitamins E and K have been amplified and a new article written on vitamin P. The use of concentrated blood serum as a diuretic is described in Chapter III. The methods of treatment of diabetes mellitus have been amended in Chapter IV and fuller details given of the pre- and postoperative care of the patient suffering from this disease. A note has been included on lipocaic. The article on gastroscopy in Chapter VI has been expanded and brought up to date. Chapter VII is a new chapter dealing with the treatment of Addison's disease. Notes have been added to Chapter X on stilbœstrol and hexœstrol. New articles have been written in Chapter XII on electro-encephalography and the use of sodium diphenyl-hydantionate in the treatment of epilepsy. Additions to Chapter XIV include descriptions of sternal puncture, heparin and plasma transfusion. The subject of the macrocytic anæmias has also been brought up to date. The method of the estimation of plasma prothrombin has been included in Chapter XV and certain methods which are less frequently employed have been omitted." The chapter on Basal Metabolism has been omitted.

E. K.

A CURRICULUM FOR SCHOOL OF MEDICAL TECHNOLOGY. By ISRAEL DAVIDSOHN, M.D., Director of Laboratories and Pathologist, Mount Sinai Hospital, Chicago; and Assistant Professor of Pathology, College of Medicine of the University of Illinois. Second Edition, revised. Pp. 47. Recommended by the Board of Registry of the American Society of Clinical Pathologists, 1942. Ball Memorial Hospital, Muncie, Ind.

STANDARDIZATION is an important need in the efficient training of medical technologists. This outline, as an excellent guide for schools of medical technology would greatly aid in this standardization.

The use of this curriculum in all schools should minimize the inadequacies of present methods and result in making technology a professional training rather than a haphazard apprenticeship which it has been in many schools of medical technology. Pathologists and technologists alike would find training in one of these schools more adaptable to their varied needs. The listed references are a thorough guide to procedures and are convenient for trained technicians as well as students. I. B.

NEURAL MECHANISMS IN POLIOMYELITIS. By HOWARD A. HOWE, M.D., Associate in Anatomy, The Johns Hopkins University, Baltimore, Md., and DAVID BODIAN, PH.D., M.D., Assistant Professor of Anatomy, Western Reserve University, Cleveland, Ohio. Pp. 234; 58 illustrations. New York: The Commonwealth Fund, 1942. Price, \$3.50.

THE studies on poliomyelitis herein collected have gained a wide reputation as being among the most important of the contemporary experimental attacks upon the disease. A reading of this book makes it obvious that the distinction rests firmly on the fact that the experiments have been planned out of a broad consideration of the disease, as it affects the individual, and as it is spread from one individual to another.

As a result of their comprehensive observations, the authors are now able to trace the main aspects of the host-virus relationships in monkeys and the higher apes. In the higher apes when the virus has been placed on the mucosa of the oro-pharynx or gut, it spreads up the nerves which supply the region, either sensory or motor, to reach the central nervous system. By critical experiments they show that the virus travels up the axonal tissue, rather than the nerve lymphatics, at a rate of 2 to 3 mm. per hour. Having reached the central nervous system, either the brain or spinal cord, the virus again follows along neuronal pathways, showing an apparent preference for the short-chain tracts. There is some reason to believe that the virus can multiply at the neuronal junctions.

The further spread within the central nervous system depends in part upon the local concentration of virus entering an area by way of converging infected neurones, and in part upon the inherent susceptibility of the neurones. Some of the nerve cells of the central nervous system are relatively immune to the virus.

Apart from these native differences in susceptibility a change may be brought about by other factors. Previous infection renders the cell immune, but the immunity to subsequent infection apparently applies only to the same strain of virus and not to other strains. In the case of the peripheral axone, changes induced by repeated section or freezing of the nerves prevents the transmission of virus up the axone.

Since the spreading virus leaves a trail behind it, and since that trail differs, especially in the early stages, depending upon the route of inoculation, the location of lesions within the central nervous system may reveal the route by which the virus entered the nervous system. Observations of this kind on human material have great importance for a solution of the problem of how the virus reaches the centers.

It has long been held that poliomyelitis travels up the olfactory nerves into the brain. This view, the authors show, is too narrow, and in the human case, may be incorrect. Their human material indicated clearly a spread from non-nasal pathways, either from the oro-pharynx or the gut. These observations, coupled with the recent findings of virus in sewage and feces, suggest that in man, poliomyelitis is primarily a gastro-intestinal disease, a view once held, but rejected by the experimental finding in the rhesus monkey that spread occurred from the nasal mucosa up the olfactory bulbs. How the virus lives in the gut and its wall is still unsettled.

Quite obviously the conclusion based on the distribution of the lesions, that the human is infected *via* the gut is of major importance, and this demonstration is one of the chief contributions of this work. G. G.

RED CROSS HOME NURSING. By LONA L. TROTT, R.N., B.S., Assistant Director, Health Education, Red Cross Nursing Service. Pp. 430; many figures and illustrations. Philadelphia: The Blakiston Company, 1942. Formerly, American Red Cross Textbook, Home Hygiene and Care of the Sick. Price, \$75.

THE Red Cross Home Nursing Book recognizes the mental and emotional sides of man's life in keeping him happy to the extent of stressing common sense values and modes of living.

Unit I is devoted to "Health and Happiness in the Home" with the basic concept of sound emotional health.

Unit II—"How the Community Protects the Health of the Home and Family," stresses the concept of man's sociability, *i. e.*, inasmuch as he is a gregarious type, certain rules and regulations must be followed for the good of the whole. Thus the part played by the County Board of Health, National organizations and their many branches is discussed. It raises the subtle feeling as to whether or not your community has access to all it might (and inquisitiveness in the right direction is a healthful sign in our democracy).

Unit III—"How to Take Care of Mother and Baby," is an excellent section. Language is clear and simple; and careful, adequate instructions are given. The book at this point is beginning to stress more fully the physical side of man's life.

Unit IV—"What to do when Sickness Invades the Home," is the section the reader has been waiting for from the title of the book. Here again, common sense and a calm emotional outlook are the factors most stressed. Simple yet effective methods of care and treatment are given—still in the clear, concise and simple language that is an outstanding feature of the book. Simple diagrams and constructive pictures add to easy readability and interest, and help in illustrating certain points to be stressed.

E. F.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 26, No. 5, Boston Number). September 1942. Pp. 306; many illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, year, \$6.00

THIS issue is a symposium on specific methods of treatment and lists among its contents articles on the present status of sulfonamide therapy, vitamins, the treatment of common forms of heart disease, hypertension, asthma, sinusitis, low back pain and the lumbosacral joint, the infectious arthritides, poliomyelitis, anemia and peripheral vascular diseases. Also to be found are pertinent articles on common laboratory aids to diagnosis

and treatment, principles of refraction, tropical medicine in the United States today and psychiatry's rôle in the prevention of neurosis.

The use of the sulfonamides engages a large and important portion of the contents and is presented with dosage, blood concentration and evidences of toxicity. It is questionable as to whether or not the use of the sulfonamides is indicated throughout the entire course of an attack of scarlet fever in view of the extremely mild character of this disease at the present time. In the treatment of cardiac asthma, the author states that ouabain may be given provided that no drug of the digitalis series has been used for at least two weeks prior to the attack. This seems overly cautious. This Reviewer feels that it should depend upon the amount previously administered. The account on tropical medicine shows the striking inadequacies of our knowledge in this field, a state of affairs which currently is being remedied in our medical schools. The article on peripheral vascular diseases is outstanding.

This issue of the *Medical Clinics of North America* is timely, well written and contains an extensive bibliography. It is worthy of the high standards of previous articles emanating from this center. L. S.

BLOOD GROUPING TECHNIC. By FRITZ SCHIFF, M.D., Late Chief of the Department of Bacteriology, Beth Israel Hospital, New York, and WILLIAM C. BOYD, Ph.D., Associate Professor of Biochemistry, Boston University. Pp. 248; 112 illustrations. New York: Interscience Publishers, Inc., 1942. Price, \$5.00.

THIS book furnishes an unusually complete, often unnecessarily detailed, account of all subjects related to the human blood groups. The subdivisions of the text include a discussion of such factors as M, N, P and Rh, the use of these factors in disputed paternity, the study of blood stains and other secretions and a consideration of the part which the blood groups play in anthropology. The text is well illustrated with charts and graphs.

W. B.

NEW BOOKS

Medical Parasitology. By JAMES T. CULBERTSON, Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 301; 19 plates. New York: Columbia University Press, Morning-side Heights, 1942. Price, \$4.25.

The subject matter of this book is divided into two main sections: (1) General Considerations, of 69 pages, in which are discussed infection, epidemiology, natural resistance and acquired immunity, diagnosis, specific therapy and prophylaxis; and (2) Infection caused by animal parasites. An appendix of technical methods, a list of "books for reference" and an index are included. Within certain limits this text is a reasonably adequate review of the field, but there is abundant evidence of hurried preparation. Many statements are indefinite, many sections are incomplete, and this is due not so much to limited space as to failure to condense material and to be concise. The book cannot be recommended. H. R.

Formulary and Handbook. Johns Hopkins Hospital. Pp. 253; many tables. Baltimore, Md.: John D. Lucas Company, 1942. Price, \$2.00.

This is a remarkably useful booklet. It includes a practically complete list of essential drugs and biological preparations needed in the practice of medicine with a brief discussion of the composition, therapeutic indications and dosage of each. Additional interest is provided by the inclusion of a large number of the formulas used in the Johns Hopkins Hospital. The material is made easily accessible not only by an excellent index but by classification according to field of usefulness, such as skin, eye, hematopoietic system, etc. The book is highly recommended to all who are not already letter-perfect in their knowledge of therapeutic agents. C. W.

Blood Substitutes and Blood Transfusion. Edited by STUART MUDD, M.A., M.D., Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and WILLIAM THALHIMER, M.D., Director, Human Serum Division, Public Health Research Institute of the City of New York, Inc. Pp. 407; many graphs. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

Changes in the Knee Joint at Various Ages. By GRANVILLE A. BENNETT, M.D., Associate Professor of Pathology, Harvard Medical School; HANS WAINE, M.D., Research Fellow in Medicine, Harvard Medical School; Graduate Assistant in Medicine, Massachusetts General Hospital; and WALTER BAUER, M.D., Associate Professor in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital; Director, Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases. Pp. 125; 31 plates. New York: Commonwealth Fund, 1942. Price, \$2.50.

Manual of Dermatology. By DONALD M. PILLSBURY, M.D., MARION B. SULZBERGER, M.D., and CLARENCE S. LIVINGOOD, M.D. Issued under the Auspices of the Committee on Medicine, of the Division of Medical Sciences of the National Research Council. Pp. 421; many figures. Philadelphia: W. B. Saunders Company, 1942. Price, \$2.00.

La Digital, Estudio Clinico, Technica del tratamiento, resultados. By DR. ALEJANDRO GARRETON SILVA, Professor titular de las Facultad de Medicina de la Universidad de Chile y Jefe de la I Seccion de Medicine del Hospital San Francisco de Borja. Pp. 143. Empresa Edit. Zig-Zag, S. A., Santiago de Chile, 1942. Price not given.

This presentation to readers of Spanish of the important facts about digitalis should be valuable in Latin America and especially in Chile, where the frequency, morbidity and mortality of circulatory diseases are high. E. K.

Advances in Internal Medicine. Edited by J. MURRAY STELIE, M.D., Welfare Hospital, New York University Division, Welfare Island, N. Y., and several associate editors. Pp. 292; several figures and tables. New York: Interscience Publishers, Inc., 1942. Price, \$4.50.

Advances in Pediatrics. Edited by ADOLPH G. DESANCTIS, M.D., New York Post-Graduate Medical School and Hospital, Columbia University, New York, and several associate editors. Pp. 306; many figures, plates and tables. New York: Interscience Publishers, Inc., 1942. Price, \$4.50.

NEW EDITIONS

Recent Advances in Medicine. By G. E. BEAUMONT, M.A., D.M. (Oxon.), F.R.C.P., D.P.H. (Lond.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton Lecturer in Medicine, Middlesex Hospital Medical School; Sometime Radcliffe Traveling Fellow, University of Oxford; and E. C. DONNS, M.V.O., D.Sc., Ph.D., M.D., F.R.C.P., F.I.C., F.R.S.E., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopædic Hospital. Tenth Edition. Pp. 440; 45 illustrations. Philadelphia: The Blakiston Company, 1942. Price, \$5.50.

Problems of Ageing. Edited by E. V. COWDRY, Washington University, St. Louis. Second Edition. Pp. 972; 129 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, \$10.00.

Sulfanilamide and Related Compounds in General Practice. By WESLEY W. SPINK, M.D., F.A.C.P., Associate Professor of Medicine, University of Minnesota Medical School. Second Edition. Pp. 274. Chicago: The Year Book Publishers, Inc., 1942. Price, \$3.00.

PROGRESS OF MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
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CHILDHOOD PNEUMONIA

DURING the past few years great progress has been recorded in man's knowledge and therapeutic control of the acute infectious diseases of the lungs so prevalent in temperate climates. For a discussion of the complete pattern of pneumonia as it appears to contemporary eyes the reader is referred to several critical books and articles.^{26,36,47,59,75} The present review restricts itself to a presentation of some of the important recent advances in our understanding of acute pneumonia as this disease is observed in the field of pediatrics.

Identification of the Infective Bacterium. Careful studies of childhood pneumonia have shown that the correlation between organisms isolated from the nasopharynx and those later cultured from blood, lung punctures, empyema fluid, pus from the middle ear and cerebrospinal fluid is much higher than with bacteria recoverable from the throat.^{4,9,13a,b,37,41} Nasopharyngeal mucus therefore is preferred to material obtained on pharyngeal swabs when searching for the causative bacterium in a child with pneumonia. Several special techniques have been developed for the purpose of obtaining good specimens for accurate typing. Auger⁶ described an apparatus consisting of a 50 cc. glass syringe connected by a short length of stiff, perforated tubing to a narrower rubber tube which can be inserted through the nares up to the adenoid area. By plugging the perforations with the fingertips when applying suction with the syringe piston, and releasing same on the instroke, a quantity of sputum adequate for identification is easily obtained. Alexander⁴ recommends a sterilized 6 inch swab made of fine copper wire with a cotton pledget rolled about one roughened tip. This is inserted into the nares, permitted to become moistened with secretion and then pushed backwards with a slow twirling motion until the posterior pharyngeal wall is encountered. The swab is left in position for about 5 seconds to collect mucus, and then quickly withdrawn. It is next placed in 0.2 cc. of pneumococcus blood broth and set immediately to the laboratory where the adherent mucus is freed before the swab is removed and discarded. The broth is used (a) to prepare poured plates, (b) to inoculate a blood agar plate and a 3 cc. tube of

blood broth, and (c) lastly for direct typing by the Neufeld method. When direct typing fails the blood broth will usually yield organisms ready for typing after 3 to 5 hours of incubation. The poured plates are prepared early in order to save time in detection of *Streptococcus hemolyticus* when present. Alexander states that if the above procedure is followed carefully the type of organism can be detected accurately in nearly 100 % of cases of pneumococcus pneumonia. *Staphylococcus aureus* and *Streptococcus hemolyticus* become evident in the poured plates after 24 hours. If the presence of *H. influenza* is suspected, diagnostic rabbit sera specific for the two types A and B should be used³ in a typing procedure identical with that used for pneumococci.

Atypical Pneumonia. During recent years an unusual type of pneumonia that differs from lobar pneumonia and the more common types of bronchopneumonia has been described in epidemic form from various parts of the United States and Great Britain. The first reports were published by Bowen¹⁰ from Hawaii in 1935, and by Gallagher³⁰ from a boys' school in Connecticut in the same year. Other outbreaks have been described among the students at the University of Oregon,⁵² Cornell University⁶⁸ and Harvard University,⁵³ at a boys' school in Massachusetts,^{30a} at a girls' school in northern Virginia¹ and also within the population at large.^{42,46,58a,60} Though the term "virus pneumonia" has been applied to the entity because of absence of positive bacteriologic findings and refractoriness to sulfonamide therapy, this designation has been severely criticized on the ground that no virus factor has as yet been demonstrated as the causal agent.

The designation "Primary Atypical Pneumonia Etiology Unknown" has been selected by the Commission on Pneumonia for reporting of this disorder within the U. S. Army.⁵⁵ From the standpoint of clinical recognition certain features are of importance. The onset is gradual over a 2 to 5 day period, with malaise, mild headache, low fever, hoarseness and soreness of the throat, intractable dry cough and muscle aching. Physical examination at this stage demonstrates merely the signs of an upper respiratory tract infection, with occasional minor lung changes such as a few scattered subcrepitant râles or partially suppressed breath sounds over the lower lobe. The spleen tip is sometimes palpable. According to Daniels,²² the cough, which is dry, metallic, non-productive and often paroxysmal, is so characteristic as to be almost pathognomonic. The blood count may show an actual leukopenia, though usually the leukocyte count at this stage is not above normal. Sputum examinations fail to yield pneumococci in significant numbers. The most striking findings are those of Roentgen ray. Chest films reveal a more extensive pneumonic process than would be suspected from physical signs. The involvement tends to be patchy, though the shadows may be uniform, resembling those of lobar pneumonia but of lesser density. In general, the lesions extend outward from the hilum but may be diffusely scattered through all parts of all lobes. The pattern is often variable, fluctuant from day to day, suggesting the presence of transitory patches of focal atelectasis.

The course of the disease is not constant. The majority of patients have a low fever for about a week or less with defervescence by lysis. In some instances the symptoms are more severe, with racking cough, cyanosis, dyspnea, prostration, leukocytosis, profuse perspiration, rela-

tively slow pulse, and spreading signs in the lung. Such an attack may last a month. Recovery is the rule, though weakness and vasomotor instability may persist for weeks. Complications such as pleurisy, thrombosis, migratory polyarthritis, meningismus and coma may occur. The pathology of the disease is obscure, since but few cases have come to autopsy, and in these the diagnosis has been questioned. The lesions as described^{42,46} were those of hemorrhagic solidification with few leukocytes in the alveolar exudate but abundant within the bronchioles. Treatment consists of supportive and palliative measures, including oxygen for cyanosis when present.

The etiology of this disorder as yet is unknown. Clear-cut transmission to animals has not been demonstrated. That bacteria are not causative agents is suggested by the failure of the patients to benefit from sulfonamide drugs. And yet the disease seems to be infectious in nature, as evidenced by the clinical pattern and the character of its spread through communities.

The differential diagnosis involves distinguishing this disorder from acute bronchitis, bacterial pneumonia and bronchopneumonia complicating bronchiectasis; from acute lung infections due to one of the influenza viruses,⁴³ psittacosis or a related virus (ornithosis),⁵⁰ "Q fever" caused by rickettsia,²³ coccidiomycosis²⁵ and toxoplasma;⁵⁷ and also from the pneumonia caused by the viruses of chickenpox,⁷³ lymphocytic choriomeningitis^{5,67} and the mongoose-infecting disease.⁷⁴ An excellent table of the differentiating criteria for pneumococcal pneumonia, atypical pneumonia and epidemic influenza is presented by Goodrich and Bradford in the August 1942 issue of this Journal.³³

It is Reimann's^{58a} view that atypical or "virus" pneumonia represents a syndrome composed of numerous etiologic entities produced by a variety of infectious agents, and that the designation "primary atypical pneumonia etiology unknown" be employed only when the etiologic factor has not been isolated or identified. The Reviewer would like to point out here that whereas every pediatrician may encounter an occasional case of such atypical pneumonia in his practice, especially during the winter months, the diagnostic facilities of the usual hospital laboratories, even those of top rank, do not possess the extensive animal colony or the skilled personnel essential for the tracking down of the many suspected, uncommon infective factors. The practitioner must wait until more adequate diagnostic services become generally available, possibly in state or regional laboratories, before he can study as thoroughly as desired his atypical pneumonia patients.

Staphylococcal Pneumonia. This type, which somewhat resembles pneumococcus pneumonia, can usually be distinguished provided thorough studies of the cases are carried out. Three important papers,^{20,21,50} recently published, throw into focus the distinctive features of this condition. Gáspár,²¹ in an analysis of 7 years' necropsy material at the Rochester General Hospital (New York) found that out of 144 autopsied cases of fatal lobar and bronchopneumonia, 38 were caused by staphylococci. Such a high proportion of fatalities emphasizes the serious character of this variety of pneumonia. Of Gáspár's cases, 20 occurred within the first year of life and 8 others from the second to the tenth year. A majority had shown symptoms of an infection in the upper part of the respiratory tract, either prior to or coincident with the

appearance of the pneumonia. Many patients developed cyanosis, particularly the newborn infants. Dyspnea, cough, dullness, fine râles and bronchial breathing were additional features. Leukocytosis was usually present. The pathologic lesions in the lung parenchyma presented morphologic variations of a more or less basic pattern. In the newborn the consolidations usually involved several lobes and often almost every part of both lungs, being dark red, hemorrhagic, sometimes mottled with gray. It seemed that in the neonatal period staphylococcic infections were so overwhelming that death ensued early. In older babies and with children who survived more than 24 hours the consolidations were red, gray-red, or gray with occasional progression of the gray spots into pinhead, pea-sized or larger softened abscesses. One baby had a diffuse capillary bronchitis, and a few showed small consolidations arranged around the small bronchi. Three of Gáspár's cases, all patients over 50 years of age, had a typically lobar-type pneumonia involving completely a single lobe. Parenthetically, a similar lobar distribution in a 1-year-old infant has been encountered by the Reviewer. Microscopically the distinctive features were: extensive hemorrhages and abscesses, large colonies of staphylococci in the bronchial exudate and in the hemorrhagic consolidations with necrosis of the surrounding parenchyma, and a paucity of phagocytic cells in the bronchial walls in spite of the violent inflammation of the overlying mucosa. Generally speaking, the whole picture was that of a spreading bronchogenic infection, having marked tendencies to tissue necrosis, abscess formation and development of empyema, all combining to produce a highly malignant type of pulmonary consolidation. Empyema was present in 14 cases, several times bilateral. The empyema was caused usually by rupture of a lung abscess into the pleural cavity, though there were several instances in which no abscesses were discovered. Pyopneumothorax and other complications such as pericarditis, parotitis and abscess of the leg were each encountered but once. One of the most common findings was the presence of an acute purulent tracheobronchitis, occasionally hemorrhagic. The exudate often caused complete plugging of the bronchi, thereby being responsible to a certain degree for the cyanosis observed during life.

Kanof, Kramer and Carnes⁴⁰ described the clinical aspects of pneumonia (staphylococcus) in the pediatric period. Their cases were subclassified as: (a) primary staphylococcus pneumonia (25 instances), and (b) secondary staphylococcus pneumonia developing in the course of staphylococcus sepsis (12 instances). Blood cultures were positive but rarely in the primary cases, whereas every patient in the secondary group had a positive culture during life. In the primary cases the history was chiefly that of an upper respiratory tract infection with subsequent downward extension of the process; in the secondary type, pneumonia was an additional and often terminal event. The mortality was 73 %, the highest being in infants under 1 year of age. Empyema was detected in 87 % of the primary cases and in 58 % of the secondary; its onset was early and the color of the fluid was often pink or red-brown. Spontaneous pneumothorax occurred but twice. The authors state that primary staphylococcus pneumonia resembles primary pneumococcus pneumonia in its predilection for winter and early spring. It is usually preceded by an upper respiratory tract infection, has an absent

or transient septicemia, exhibits an acute onset, fastigial temperature curve, physical findings indicating a lobar type of consolidation and leukocytosis, and gives rise but rarely to distant pyogenic localizations. Certain significant distinctions differentiate the two kinds of pneumonia—in the staphylococcus cases the age of the patient is usually below 1 year; the onset and course in a child previously healthy are more often fulminating although with chronic illness the onset may be insidious and unsuspected; empyema is extremely likely to develop; the character of the empyema fluid may indicate destruction of tissue with bleeding into the pleural cavity; pyopneumothorax may be superimposed; the patients have marked tendency toward diarrhea, abdominal distention and renal symptoms; and finally the mortality is overwhelmingly greater than with pneumococcus pneumonitis.

In a presentation of 6 cases, all ending fatally, Clemens and Weens²⁰ emphasize the serious nature of staphylococcic pneumonia in infants. Empyema occurred early in all, complicated by pneumopyothorax in 4. The physical diagnosis of pneumopyothorax in young infants, though exceedingly difficult, should be suspected if the patient manifests the sudden development of cyanosis, hyperpyrexia, increase of cardiac and respiratory rates and vomiting of dark brown gastric material. Frequent roentgenologic examinations are advised in all suspected cases. If roentgenograms are taken with the sick child in the upright position, horizontal fluid levels or air may become demonstrable at the periphery of the affected chest cavity. Adhesions between parietal and visceral pleura form rapidly in staphylococcic empyema, preventing complete secondary collapse of the lung by the positive intrathoracic pressure, and protecting against shifting of the mediastinum and downward displacement of the diaphragm. Treatment by thoracentesis should be instituted early, along with chemotherapy, antitoxin, blood transfusions and maintenance of proper fluid balance.

Staphylococcic Pneumonia and Epidemic Influenza. No presentation of the current views on staphylococcus pneumonia would be complete without some discussion of its importance as a complication of influenza. That there may be a significant association between the two diseases has long been appreciated. On empirical grounds alone, the *Staphylococcus aureus* has been considered for years one of the most virulent of the secondary invading bacteria in terminal pneumonia complicating epidemic influenza.^{17,76} The direct recovery of influenza virus from such fatal cases has been carried out but a few times, by Seadding⁶² and by Stokes and Wolman.⁷¹ Other evidence for the presence and activity of influenza virus in staphylococcus pneumonia has been supplied by Finland, Strauss and Peterson²⁷ and by Michael,⁵¹ who were able to demonstrate either a very high titer or a decided increase in protective antibodies against influenza virus in patients suffering or recovering from staphylococcus pneumonia. During the course of epidemics of influenza in their communities all such cases were of adult age. It is extremely likely that children could be similarly affected, although, working with Dr. Werner Henle, the Reviewer has failed to recover this specific virus from the lungs of a number of fatal cases of staphylococcic pneumonia studied in Philadelphia during the past few years. Nevertheless, the available evidence suggests strongly that many of the cases of so-called primary staphylococcus

pneumonia encountered in childhood are best considered as being complications or developments secondary to invasion of the respiratory tract by the viruses responsible for catarrhal upper respiratory tract infection, such as the common cold and the epidemic influenza viruses.

Cellular Inclusions. Goodpasture, Auerbach, Swanson and Cotter³² discovered nuclear inclusion bodies within the epithelial cells of the trachea and bronchi and their mucous glands and of the alveolar epithelium in 5 cases of pneumonia complicating measles or whooping cough. Rapid necrosis of the affected cells was occurring, resulting in ulceration of the epithelial surfaces. The associated bacterial infection of the lungs was considered as a secondary invasion. The authors suggest that the appearance and distribution of the inclusion bodies is indicative of the presence of some unknown virus as the causative agent, even though experimental inoculation of infected lung tissue into various laboratory animals failed to induce any evidences of infection.

A similar chain of reasoning has prompted Adams¹ and Adams, Green, Evans and Beach² to attribute 2 outbreaks of acute primary pneumonitis among infants in Minnesota to an unknown inclusion-producing virus. These authors studied 74 cases from these two epidemics and found that the disease manifested a constant symptom pattern characterized by cough, dyspnea, cyanosis and low-grade fever. The mortality was 20%. No bacteriologic agents considered etiologically significant were disclosed in either epidemic. Uniform pathologic changes were found in the lungs from fatal cases, namely, cytoplasmic inclusion bodies in epithelial cells, sloughing and proliferation of bronchial epithelium, accumulation of mononuclear exudate and patchy atelectasis. In 20 control cases of pneumonia in infants caused by ordinary bacteria, these pathologic changes did not show nor were inclusion bodies seen. Of the sick infants, 85% showed the presence of inclusion bodies within epithelial cells stained in throat smears, whereas less than 10% of infants and adults in 5 control groups showed inclusion bodies. Fairly extensive biologic studies on the nature of the etiologic virus were carried out but these failed to isolate the agent. Prematurely born and newborn infants were the most susceptible. The authors state that no specific therapy has been developed as yet for this form of primary pneumonitis. General measures, such as the administration of oxygen, postural drainage, aspiration of exudate, blood transfusion, and therapy with the sulfonamide drugs (to combat secondary bacterial infections), appeared to be efficacious in some cases. Whole adult blood may have prophylactic value, especially in the premature infant.

Peripheral Circulation. Greene³⁴ attacked the problem of circulatory failure sometimes seen in the more serious attacks of lobar pneumonia from the standpoint of developing changes in the peripheral circulation near the time of crisis. The blood pressure and the reactions of the small blood-vessels of the skin were studied in a group of 52 children with pneumonia. The blood pressure was found to be raised during the acute stage of the disease, definitely lowered at the time of the crisis and increased again during convalescence. In none of the patients who died was there any significant fall in blood pressure during the course of the disease nor toward the end. The reactions of the small vessels of the skin showed an impaired efficiency at the height of the

disease in the contractility of the capillaries, which returned to normal in a short period after the crisis in those patients who recovered. In the patients who died, this impairment of the ability of the capillaries to contract became greater and continued to the time of death. Greene thus corroborated the earlier conclusions of Ritchie⁶¹ and of Perry⁵⁶ on adult patients, that therapy in such cases lies in the direction of stimulating and improving the tone of the minute blood-vessels rather than in attempts to increase the efficiency of the heart itself.

Localized Bullous Emphysema. The precise nature of the cavity-like formations occasionally seen in chest films subsequent to pneumonia has become elucidated by a number of recent clinical studies.^{18,45} Although the majority of papers deal with findings in adults, there have been enough reports on children, notably that of Childe and Benjamin,¹⁷ who observed 19 instances, to indicate that the disorder can be present at all ages, with perhaps a greater tendency to expansile behavior in the first years of life.

Clinically the lesion as seen in the roentgenogram consists of a thin, rather sharply defined smooth annular shadow, almost like a white pencil line, surrounding an air-filled space of decreased density in which lung markings are diminished or absent. By means of stereoscopic, lateral, and oblique roentgenograms one can demonstrate that these clear spaces are spheroid, ovoid or loculated. Occasionally they contain a small amount of fluid and show a straight line fluid level in the upright position. They vary in size from time to time and may persist for as long as 8 or 10 months before fading away. They are not accompanied by any abnormal signs or symptoms unless enormous inflation results or unless the pleura ruptures with the formation of a large positive pressure pneumothorax. The differential diagnosis between bullous emphysema and lung abscess, localized pneumothorax, congenital pulmonary air cyst and diaphragmatic hernia is not difficult if the course of the case can be followed for a short time. According to the consensus of published articles, the clear central portion of these pseudocavities consists of hyperdistended bullous lobules or groups of lobules with ruptured or unruptured septa between them, while the peripheral ring-like line of increased density represents a surrounding zone of atelectatic alveoli. This explanation no doubt holds in the majority of instances. Kessel,^{41a} however, has suggested that some may be true lung cavities, the end-result of a putrid pulmonary necrosis. The Reviewer has followed several typical cases through to autopsy and discovered evacuated abscesses of staphylococcus pneumonia having narrow valvelike bronchi coursing through their walls. Benjamin and Childe suggest that the most probable explanation for the formation of localized bullous emphysema in association with pneumonia is the plugging of a bronchiole with mucus or exudate, producing an obstruction of ball-valve type. Air enters the affected lobule or groups of lobules more readily than it can emerge, resulting in emphysematous dilatation. Secondary kinking of the bronchiole helps to accentuate the obstruction. Rupture of the alveolar walls may occur and air may track subpleurally or intrapleurally, forming a voluminous balloon-like emphysematous space. If the pressure rises sufficiently the pleura can rupture, giving rise to pneumothorax. No treatment is necessary unless complicating conditions ensue. Aspiration of air by needle and syringe usually gives

but momentary clearing but should be attempted in the presence of respiratory or cardiac embarrassment, especially if a complicating pneumothorax has appeared.

Empyema. The clinical picture of postpneumonic empyema in childhood has been much changed by sulfonamide therapy, according to Burford and Blades.⁸ The incidence of this complication has been reduced from approximately 5%^{36,38} in the presulfonamide era down to 1% or less.^{14,39,64} Furthermore, Burford and Blades found that the course of postpneumonic empyema becomes atypical and bizarre in sulfonamide-treated patients. The transition from effusion to thick pus is prolonged, the incidence of interlobar empyema seems higher and there is a greater tendency for the formation of encapsulated pockets which are difficult to detect and to drain adequately. Reëxpansion of the lung and obliteration of the pocket may be slower, and the authors noted an increase in the required number of thoracotomies per individual patient. They advise that chemotherapy be stopped once the initial pneumonia has been adequately controlled, even if pus has accumulated. The sulfonamides with their antipyretic properties and anorexic effects not only fail to penetrate the purulent accumulations, but serve to confuse a clinical picture already difficult enough. Surgical drainage remains the treatment of choice for purulent empyema.

Subacute Pneumonia. Somewhat resembling "atypical pneumonia" is a subacute form of pneumonia described by Lincoln, Smith and Kirmse.⁴⁴ The attack, as observed at Bellevue Hospital, New York, commences with nasopharyngitis or sinusitis and cough. After some days or weeks the cough becomes worse and more productive, a low fever develops, and thoracic pain appears, worse on inspiration or cough. Physical signs in the chest consist of diminished breath sounds, usually at the bases, in association with resonant râles. The characteristic Roentgen picture is an irregular shadow extending from the hilar region, usually downward along the cardiac border and across the diaphragm. The shadow is not as homogeneous or dense as that of lobar pneumonia, and often shows bronchial streaking or uneven mottling. Usually the cardiohepatic angle is obliterated and there may be enlargement of the hilar nodes. A moderate leukocytosis will persist for 2 to 3 weeks after the onset of recovery. Sputum is abundant and purulent, varying in amount from a few drams to 8 ounces or more. Many organisms are present but the types of pneumococci usually associated with lobar pneumonia in childhood are not found. Collapse of a lobe secondary to bronchial plugging by tenacious mucus may be clearly evident. The illness lasts from a few weeks to several months, and may recur. The prognosis for life is good. Since none of the cases succumbed, the exact pathology of the disorder remains obscure. As a rule the child makes a complete recovery, though residual bronchiectasis has been observed. Therapy consists of local treatment of the associated upper respiratory tract infection and postural drainage of the bronchial tree, to be followed by bronchoscopy in severe cases or when collapse of a lobe occurs. Chemotherapy is not mentioned in the presentation but should be intelligently applied. Cases which do not clear completely should have a bronchogram before the diagnosis of bronchiectasis can be excluded. The picture of this disorder as presented by the

authors closely resembles the more familiar one of obstructive pulmonary lobe atelectasis or "massive collapse" due to tenacious sputum, occurring in the course of tracheobronchitis.

Chemotherapy. The efficacy of sulfonamide therapy in childhood has been established by a great number of reports from clinics in all parts of the world. Observers of a few years back contrasted the complication and mortality rates of the pre- and postsulfonamide years, whereas the more recent papers are devoted to controlled comparisons of the results obtained with the different sulfonamide derivatives. A statistical summary and interpretation of the reported data would necessitate an unduly long review.

One can summarize the current observations and trend of pediatric thought in this field by stating that, with sulfapyridine and sulfathiazole, recovery from pneumonia is aided and accelerated, and complications are not frequent or as a rule troublesome.^{7,19,29,35,48,63,64,65,69,70,72} "Both drugs have so altered the course of pneumonia that few of the long, hard cases with cyanosis, delirium, abdominal distention and circulatory failure are seen."⁶⁴

Sulfapyridine, sulfathiazole and sulfadiazine are in wide use at present in the treatment of pneumococcic pneumonia. Reports of sulfadiazine in pediatric journals are scarce because of the newness of this compound, but the literature of the coming year should contain a number of reports on its efficacy. For hemolytic streptococcus pneumonia, sulfanilamide may be employed; but in a doubtful case sulfapyridine or sulfathiazole should be given, as these latter substances are effective against both streptococcus and pneumococcus. For staphylococcus pneumonia, as with such infections elsewhere in the body, sulfathiazole is the drug of first choice. Unfortunately its therapeutic action against the staphylococcus is much weaker than against pneumococcus or streptococcus.

As for the relative merits of sulfapyridine, sulfathiazole and sulfadiazine, it is questionable if in promptness of action there is any significant difference among these three drugs. In childhood as with adults, much more nausea, vomiting, cyanosis, dizziness and headache and general discomfort are encountered with sulfapyridine than with the other two products. Sulfathiazole and sulfadiazine are therefore to be preferred. With all three drugs toxic reactions must be watched for, such as hematuria, dermatitis, fever, jaundice and urinary tract obstruction from precipitated excretory products, even though the incidence of such untoward effects is not great. The primary treatment of any of these complications consists in discontinuance of the drug.

As a single illustration of the success in therapy achieved by the sulfonamide drugs one can cite the experience of Greengard, Raycraft and Motel³⁵ with infants under 1 year of age. In 1937 and in 1938 the mortality among infants with pneumonia treated in the Children's Division of Cook County Hospital was 32% and 31% respectively. In 1940 in a series of 200 infants treated with sulfapyridine the mortality was but 10%. If the cases in which death occurred in 24 hours are excluded, the mortality was 7.5%. Of a series of 89 patients, of whom 46 received sulfapyridine and 43 served as controls, those treated with the drug showed a definite reduction in duration of the febrile period

and length of stay in the hospital. In 1939 there were 89 patients, of whom 46 received sulfapyridine and 43 served as controls. Those treated with the drug showed a striking decrease in the duration of the febrile period, in the incidence of extension to other lobes and in the length of stay in the hospital.

Serum Therapy. Although the use of type specific horse or rabbit serum is no longer considered the most desirable form of therapy of pneumococcic pneumonia in childhood, mention should be made of at least a few of the excellently controlled studies on serum treatment which were carried out in the years immediately preceding the introduction of the sulfonamides. Nemir,⁵⁴ Bullowa,^{11,12} Kereszturi and Hauptmann⁴¹ all described marked reduction of mortality, particularly in cases with bacteremia, decrease in the incidence of complications such as empyema, and dramatic shortening of the course of the disease. Especially with pneumonia caused by pneumococci of Types I and XIV, the corresponding therapeutic sera proved strikingly effective. The earlier in the course of the infection that treatment was instituted, the less likely became the subsequent development of secondary complications.

The disadvantages of serum therapy have been well epitomized by Hodes and associates.³⁷ Since the type of pneumococcus must be determined before serum can be given, difficulties in typing may cause serious delay in the start of therapy. When more than one type of pneumococcus is recovered from a patient's nose or throat, it is not possible at the beginning to be certain which organism is causing the pneumonia. Moreover infants and younger children are too young to be coöperative and are disturbed and excited by the administration of the serum. Again, despite all precautions, serious serum reactions, though infrequent, do occur occasionally. The child who received serum will very likely become sensitized to the serum of the animal used. And since the mortality rate even for untreated acute primary pneumonia in infants and children is low, the use of a specific form of therapy which has certain dangers is subject to criticism, even though the incidence of untoward reactions is not frequent. Finally in contrast to the relative cheapness of the sulfonamide drugs, the cost of treating a patient with serum is much greater.

The problem of whether to treat children with pneumonia by the joint use of sulfapyridine or sulfathiazole and specific antipneumococcus serum or solely by drugs has been discussed by Carey,^{14,15,16} who noted in a study on 613 children with pneumonia that the giving of the two types of remedies in combination seems to possess some slight advantage over the use of drugs alone. The average duration of pneumonia after joint treatment had been started was a little shorter than with chemotherapy alone, and recurrent pneumonia was not observed in any patient who had received combined chemotherapy and antipneumococcus serum. He concluded, nevertheless, that routine administration of serum is not indicated except in the presence of pneumococcus bacteremia, of widespread involvement of the lungs with pneumonia, of severe toxicity from the infection or of allergic sensitivity to the sulfonamides in a patient profoundly sick.

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GYNECOLOGY AND OBSTETRICS

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URINARY INCONTINENCE

SHAKESPEARE¹⁴ described an unseaworthy vessel to be "as leaky as an unstanched wench." Those of us treating urinary diseases in women know that an "unstanched wench" can be constantly wet, thoroughly miserable, and a social outcast. The degree of urinary leakage may vary from an occasional accidental wetting when with a full bladder the intraabdominal pressure is suddenly raised by sneezing or coughing, to the pitiful spectacle of complete and constant incontinence. The lesion causing this condition may be above, at, or below the vesical sphincter. In this discussion examples will be presented with a survey of recent suggestions as to management.

Vesicovaginal Fistula. A fistulous opening between the vagina and the bladder is usually due to either pressure necrosis as the result of a long and difficult labor or to an injury to the bladder in the course of a pelvic operation. Such lesions are not nearly so common as formerly, in large measure due to greatly improved obstetrics. Many operations for the closure of these fistulas are conducted without adequate urologic study and certain types of fistulas, which might be closed by simple urologic treatment, are frequently subjected to extensive surgical procedures. Multiple operations often reduce the size of the fistula without effecting closure, and it is generally recognized that the frequency of healing decreases after each operation.

O'Connor¹¹ writes of the possibility of closing less extensive defects by cystoscopic and vaginal coagulation of the tract and proper prolonged

postural drainage of the bladder by means of an indwelling urethral catheter. If the fistula is small and has healthy surrounding tissue it will heal after electrocoagulation. He believes that this method should receive more consideration, especially in patients in whom an unsuccessful surgical repair has resulted in a small lateral opening. The method has no place in the treatment of fistulas of the bladder floor or in patients with extensive tissue defects. When the fistula is small and the bladder can be distended with fluid, cystoscopy can be done without any difficulty. But when the fistula is large and the fluid introduced into the bladder runs out of the fistulous opening as fast as it can be introduced, cystoscopy is impossible. To overcome this, Duncan³ infiltrates the vaginal introitus with procaine solution and passes a subcuticular suture of heavy silk or linen around the entire vaginal outlet and ties it very tightly to make the vagina watertight. Before cystoscopy is begun the bladder is irrigated with boric acid solution, a bivalve speculum is introduced and the vagina is dried out, taking care not to cause bleeding from the sensitive bladder mucosa that protrudes through the fistula. The introitus is then closed with the subcuticular suture. A bladder that has been decompressed over a long period of time will be hard to distend, but as the bladder and vagina are distended together, the fistulous opening can be viewed and its relation to the ureteral orifices noted so that they may be avoided in any operative procedure that is to be undertaken. When the fistula is small but the patient voids a fair proportion of urine by urethra, a ureteral catheter can be passed through the fistulous opening from the bladder into the vagina and quickly drawn through. The catheter should be slightly rough from age or repeated sterilization. Passage of such a catheter causes a fresh abrasion of the tract which then may heal quite readily. For the treatment of a large fistula at the vaginal vault in old women, following either hysterectomy or irradiation, he suggests the employment of total colectomy after closure of the fistula. This procedure can only be done where the cervical canal is completely closed from irradiation or after panhysterectomy. After operation for the ordinary fistula well above the bladder neck he keeps an indwelling Pezzet catheter in the bladder for from 7 to 10 days. When the fistula is low down near the bladder neck, a plain catheter is sutured in place. When the patient has had repeated unsuccessful operations, a suprapubic cystotomy with a large Pezzet catheter is a satisfactory method of drainage.

Halban⁵ of Vienna has had increasing satisfaction with his results in the operative cure of this condition which he attributes to a simplification of his technique and adherence to three basic principles, *viz.*, extensive exposure of the fistulous area, mobilization of the base of the bladder, and correct suture. The exposure of the field is accomplished by the correct application of posterior and lateral retractors. If the vagina is narrow, or the perineum is high and rigid, or if the fistula lies deep in the vaginal funnel, an episiotomy or a Schuchardt incision is made as a preliminary procedure, thus gaining a tremendous increase in the exposure. The base of the bladder can be adequately exposed only if it is movable and in many cases with extensive scarring in the parametrial and paravaginal tissues, it will require tedious dissection to mobilize the bladder. The fascia should be allowed to remain on

the bladder and separated with it from the vagina. In placing the bladder sutures he ignores the fistula itself but sews the anterior and posterior portions of the mobilized bladder floor over the fistula. These two portions with their attached vesicovaginal fascia are united by fine catgut sutures in areas uninjured by scars or dissection, usually about 1 cm. from the margin of the fistula. This may be buried with a second row although he states it is unnecessary and the vaginal mucosa may be sutured over this, although here again he states that it is immaterial. Occasionally it may be easier to place the sutures sagittally rather than transversely, but the tension is usually less in the latter plane. Its essential point is to sew healthy bladder wall to healthy bladder wall, taking about one-half the thickness in the suture and not too close to the fistula.

As evidence that good results in the cure of this condition may require more than a single operation, the report of Pemberton, Smith and Graves¹² is of interest. In their series of 100 cases cures were obtained in 84 % although it was necessary to perform 38 repeat operations. The use of silver wire as advocated by Sims many years ago is considered one of the most important factors in achieving a cure in their clinic. The wire is used as interrupted sutures and includes a good bite of all tissues down to the bladder mucosa. It gives good support, does not cut through and causes little irritation. It is left in for at least 3 weeks and usually for from 4 to 6 weeks. After operation the bladder must be free from tension and an indwelling catheter is left in place for from 9 to 14 days, keeping close watch that it does not become obstructed. The sutures are usually removed under anesthesia. In general, the authors believe that it is not wise to attempt to close a fistula as soon as it occurs because some will close spontaneously. Fistulas due to irradiation should not be operated upon until the tissues have had time to recover from the treatment, which is at least a year. The authors warn that one should not be discouraged if the first operation is unsuccessful as some cases required as many as 6 operations before a cure is obtained.

From his experiences at the Mayo Clinic, Counsellor^{1a} states that a fistula which involves the posterior margin of the internal vesical sphincter is one of the most difficult of all to close. The sphincter is torn and partially incompetent as a result of formation and contraction of scar tissue within the circular muscular fibers. It is difficult to avoid superimposing the vaginal and vesical suture lines at this point without producing distortion of the sphincter and urethra and it is well known that apposition of these suture lines predisposes to recurrence. Furthermore when a catheter is inserted through the urethra into the bladder it is almost certain to lie in contact with the region of repair. The catheter produces irritation and incites infection with possible breakdown of the suture line. For this reason Counsellor encourages such patients to arise and void voluntarily if possible, since the passage of urine over the small repair in the sphincter is more beneficial than detrimental since all sediment and exudate are thus lavaged periodically from the suture line. When a patient cannot void as suggested, the bladder should be emptied for a few days by a glass catheter. A fistula involving the ureteral orifice creates an interesting surgical problem since the kidney and ureter are complicating factors. Frequently there

is partial obstruction to the flow of urine and as a result hydronephrosis of some degree, with partial destruction of the kidney and small cortical abscesses may be present. Counseller does not believe that reimplantation of such a ureter into the bladder is justified, particularly if the kidney on the opposite side is normal. Nephrectomy with secondary closure of the fistula is his procedure of choice. However, if the opposite kidney is not normal, a skin ureterostomy should be considered to see if the kidney will recover sufficiently to permit implantation of the ureter into the bladder or rectum at a later date. Whenever the kidney and ureter are normal, the ureter should be reimplanted into the bladder well away from the fistulous tract and at the same time the vaginal fistula should be closed. Any attempt to repair such a fistula without diversion of urine from the involved ureter will result in a high incidence of failures. Fistula adjacent to but not involving the ureteral orifice should be repaired by the vaginal approach after inserting a No. 6 or No. 8 ureteral catheter into the ureter. The catheter should remain in place for from 5 to 10 days after the repair. Fistula in the posterior wall of the bladder is the most common type of fistula subsequent to abdominal hysterectomy. Counseller explains that it is not caused by an unrecognized incision into the bladder, but from a suture which catches the mucosa of the bladder, gradually cuts through and produces a fistula 8 to 10 days later. Repair of a fistula caused by treatment with radium is less likely to be successful than fistulas caused by trauma because the tissue at a considerable distance from the edge of the fistula usually is too devitalized for use in the repair. Any attempt at repair should be delayed a sufficient length of time to preclude the possibility of local recurrence of the malignant process. In most instances the fistula will become smaller from contraction and should it reach the size of a pin point, it may be closed by fulguration.

It is readily understood that urinary fistulas are more commonly seen among primitive people than in this country where good medical facilities are generally available. Whereas in this country cases might be reported by the dozen, in some of the overpopulated countries of the Near and Far East, surgeons report such cases by the hundreds. Probably no one has had a greater personal experience with this problem than Mahfouz⁹ of Cairo, who reports on nearly 500 cases. In the ordinary types he uses spinal anesthesia, makes a circular incision around the fistula and widely mobilizes the bladder. He then inverts the bladder opening with catgut sutures which do not penetrate the mucosa and the vagina is closed over this with silkworm gut sutures. A retention catheter is left in for 7 days. He describes his method of handling various complicated and difficult cases, the essential points being good exposure and lack of tension on the suture line. He had tried the suprapubic approach in some cases but uses it no longer as he considers the vaginal route safer. He found that if he failed to close a fistula by the vaginal route he also failed by the suprapubic route. He frankly admits that some fistulas are not curable and in such cases colpocleisis or ureteral transplantation may be used, but he does not advise either one on account of the danger of ascending infection of the urinary tract. He advised such patients to wear a rubber urinal. He advises that before any operation is performed in these cases, the vagina, bladder and kidneys must be put in healthy condition.

In his practice among the Zulus, Taylor¹⁶ has found many vesicovaginal fistulas which show enormous loss of tissue and tremendous scar formation. Many of these can be cured by extensive flap dissections although often incontinence may remain due to loss of the sphincter muscle. In cases in which a plastic operation cannot be done due to the extensive destruction and in which transplantation of the ureters would not be justifiable, he has devised an interesting operation to be used if the cicatricial condition of the vagina precludes further sex life. The vaginocutaneous junction is incised completely around the outlet and flaps of vagina and skin are dissected up. The vaginal flaps are sewn from side to side so as to invert them and close the vagina and the skin flaps are united over them with an everting stitch. Before the sutures are tied a stab wound is made through the anus just anterior to the anal margin and a long forceps is pushed through the sphincter and cut down on from the posterior vaginal wall about 1 inch above the vaginal cutaneous junction. A medium-sized catheter is pulled through the tract thus made, anchored by a stitch and cut off leaving $\frac{1}{2}$ inch projecting into the vagina and also on the skin surface. The catheter remains for 6 weeks in order to allow epithelialization of the tract. The vagina then acts as a urinary receptacle which spills over into the rectum which is controlled by the anal sphincter.

From his experiences in India, Hayes⁶ stresses that any associated rectovaginal fistula should be cured before an attack is made upon a vesicovaginal fistula. After this the infection in the bladder and vulva should be overcome by boric acid irrigations and sitz baths. At the operation a single or double Schuchardt incision may be necessary to obtain adequate exposure. The bladder must be thoroughly mobilized so that there will be no tension on the sutures. Contrary to many other opinions, he warns against excising the edges of the fistula. He uses these edges as anchorages for the closing suture, applying two layers of No. 00 20-day catgut. After operation he drains the bladder by a self-retaining catheter for at least 10 days and irrigates the bladder twice daily. Of 33 cases operated upon this method he obtained 28 cures.

Suprapubic Approach. Thus far in this discussion we have considered only the vaginal approach for the repair of vesicovaginal fistulas. There can be no doubt that this method is the most commonly employed as well as the oldest type of approach. However there are some authorities who feel that in certain types of fistulas a safer and better operation can be done if the site of the fistula is approached from above the pubis. Such an operation may be transvesical and extraperitoneal or it may be transperitoneal. A firm advocate of the transvesical operation is Quinby¹³ who states that the object of an operation for vesicovaginal fistula is to get a tight bladder. The bladder must hold urine, the vagina cannot. Closure of the bladder should be as perfect as possible, whereas closure of the vagina is a secondary consideration and need not be perfect because it will heal by granulation. He believes that the easiest and most complete access to the bladder is by the suprapubic route and it should be employed in all but the simplest cases. Sufficient mobilization of the floor of the bladder from the vagina is imperative. If necessary this can be facilitated by splitting the whole detrusor portion of the bladder in a sagittal direction. Open-

ing of the peritoneal cavity during the operation is not dangerous if the subsequent repair of the bladder is perfect. Quinby advises that serious and extensive loss of bladder tissue with dislocation of the ureters and much scarring is in most instances treated by bilateral ureterosigmoidostomy. Farsht,⁴ in reporting his series of 20 cases of suprapubic transvesical repair, observes that fistulas of surgical origin are on the increase while those of obstetrical origin are on the decrease. The fistulas of surgical origin are, as a rule, fixed high up in the vagina and are in close proximity to the ureters. The inaccessibility of these fistulas from the vagina approach makes their exposure, proper dissection and repair very difficult. It is Farsht's belief that the transvesical approach gives good exposure, allows careful dissection of the fistulous tract, prevents unsuspected injury to the ureters and permits suprapubic drainage of the bladder which, in his opinion, is superior to any other type of vesical drainage. At the Mayo Clinic according to Hubly and Masson⁷ the vaginal route is and will remain by far the most common and desirable of approaches but the suprapubic operation is used in 11% of the cases. They prefer the transperitoneal operation when operating from above but they admit that their indications for this operation are not standardized. Usually vaginal plastic procedures have been tried and have failed before the abdominal approach is attempted. Vaginal repair may be very difficult following a total abdominal hysterectomy if the vault of the vagina is scarred, narrowed and retracted and the fistula is situated in the vault. Vesico-utero vaginal fistulas in the absence of prolapse are most difficult to repair through the vagina, but are readily accessible from above, while in cases of large fistulas situated in the base and trigone of the bladder and adjacent to the ureters the danger of injury to the ureters is less with the abdominal approach. Furthermore with this approach if the ureter is injured, it may be reimplanted into the bladder or transplanted into the sigmoid at the time of repair. In this operation a low midline incision is made, the patient placed in the Trendelenburg position and the intestine and omentum are pack out of the way. The uterus is drawn upward, exposing the vesico-uterine reflection of peritoneum which is cut transversely sufficiently far on each side to afford easy separation of the bladder from the anterior wall of the cervix and vagina. The dissection is carried out until the fistula is reached and extended below this point in order to freely mobilize the bladder wall and vagina around the fistula. The fistula is cut across and the edges of the mucosa are inverted into the bladder with interrupted sutures of No. 00 chromic catgut, taking care not to penetrate the bladder wall with the sutures. The opening in the vagina is closed in a similar manner and if possible in the opposite direction and care is taken to prevent contact of these two wounds. Sometimes it is advisable to insert a small free graft of omentum but in most cases a strip of peritoneum can be interposed. If the opening in the vagina is in close contact with the cervix, freer mobilization is obtained by doing a total hysterectomy at the same time. If this is done the sigmoid or an epiploic appendage from it can be interposed between the bladder and the vaginal closure. Treatment of infection of the lower urinary tract may be started early in convalescence. Mandelic acid or sulfanilamide therapy is very satisfactory. When the fistula has been of long duration the capacity of the bladder

is reduced. This may be corrected by gradual dilatation of the bladder but not before 3 months after operation. Likewise sex life should not be resumed before 3 months have elapsed.

Transplantation of the ureters to the sigmoid flexure is a sound surgical procedure for the treatment of huge vesicovaginal fistulas according to Counseller.¹⁶ The operative risk is decreased when one ureter is transplanted at a time. Before doing this operation several factors must be considered, namely, the general physical condition of the patient, whether there is any obstruction or infection of the upper urinary tract, the function of both kidneys, the presence or absence of pelvic cellulitis which involves the lower end of the ureters, previous surgical procedures in the pelvis which may have resulted in fixation of the pelvic portion of the colon and the preparation of the patient for a colonic operation.

If the ureter is partially obstructed, ureterectasis, pyelectasis, thickening of the ureter and infection rapidly supervene and experience has shown that one assumes a great risk in transplanting a ureter of this type. In such instances, if the ureters are known to be thickened and partially obstructed, he believes that it is wise to perform bilateral nephrostomy first and several weeks later, when infection has subsided, the ureters can be transplanted with considerably less risk. The introduction of intravenous urography has been beneficial in the study of the excretory function of the kidneys before and after transplantation of the ureters.

Relaxed Vesical Sphincter. Thus far we have been discussing leakage of urine due to an abnormal opening in the bladder. In contrast to this type of incontinence, there is a type of leakage which is not constant but occurs intermittently, usually when the bladder is partially distended. This is due to a weakness of the vesical sphincter. These patients complain that leakage is most common when intra-abdominal pressure is suddenly raised, as in coughing or laughing. Hence the term "stress incontinence" is frequently applied to this condition. The lesion is usually due to a childbirth injury in which the supporting structures of the vesical neck have been torn, the resulting lack of support causing interference with the normal sphincteric mechanism. Murless¹⁰ has treated 20 such patients by means of local injections of 5% solution of sodium morrhuate with cure in 60% and marked improvement in 25% of the cases. Patients with only a slight degree of prolapse have the best chance of cure. Although only small quantities of the morrhuate solution were injected, never more than 0.5 cc. on either side of the urethra, a slough separates in the vast majority of cases, but this seems to favor a good end-result by causing scarring. The expected dangers of sloughing urethra, collapse during injections and urethral stricture have not occurred. This method would appear to have value in those cases with slight prolapse, those following a repair of prolapse but without recurrence of the prolapse itself, and in old patients in whom operation should be avoided.

In intractable cases of urinary incontinence due to loss of sphincter control in which no urinary fistula is present, Stanca¹⁵ advocates the Goebell-Stoeckel technique of repair. An incision 12 cm. long is made in the midline extending to the symphysis. The aponeurosis is freed on each side and a flap 4 cm. broad and 10 cm. long is cut, including the insertion of the pyramidalis muscle but left attached at the sym-

physis. This flap is then split down the center, making two strips, the upper surface of each being fascial, the undersurface being muscle. Through the opening from which the flap was elevated, channels are made by blunt dissection behind the symphysis and under the urethra. The two fascial strips are crossed and then directed down these channels. From the vaginal approach the anterior vaginal wall is incised, the urethra freed and the fascial strips brought down from above and sutured under the urethra. Both vaginal and abdominal wounds are closed and a retention catheter is placed in the bladder for 6 days. As a result of this transplantation, the pyramidalis muscles reinforce the fibers at the internal sphincter and also elevate the neck of the bladder, both of which actions tend to prevent urinary incontinence.

Kennedy⁸ has made an interesting study of the condition by means of pre- and postoperative urograms. He found that the normal urethra in its voiding state is pushed down with the vaginal wall into the vagina, its external meatus is pushed endwise out of the pelvis by varying distances up to 1 cm. and the sphincter muscle surrounding the inner third of the urethra dilates. A varying degree of the "voiding" state (which becomes permanent following relaxation or injury) is present when there is persistent incontinence; the greater the degree the greater the incontinence. When there is no permanent dilatation of the inner third of the sphincter, the urethra may undergo excessive degrees of motion without any incontinence. However, persistent displacement may in time permanently overstretch the inner third of the sphincter, when incontinence will develop. The sphincter mechanism functions with its greatest efficiency when its greatest length is restored, particularly as far as possible within the pelvis and as high as possible above the vagina. To accomplish this restoration it is necessary to separate completely the urethra from all attachments to the vagina wall and the rami, after which the sphincter mechanism can be restored by plicating and replicating the undersurface of the bladder and urethra. Any factor such as infection or hematoma beneath the restored urethra may dissolve the plicating sutures and allow the urethra to resume some degree of the "voiding" state, thereby producing failure, necessitating another operation. Therefore there should be free drainage of the paravesical spaces after operation. Kennedy urges that a very sharp distinction be made between urinary incontinence and urinary urgency or frequency to avoid operations upon patients with the latter complaints but no incontinence. He also advises that the physician should be frankly honest with incontinent patients, explaining clearly that the first operation may be unsuccessful and a second one required.

Ectopic Vaginal Ureter. At first thought, it might seem impossible for a patient to be incontinent when there is no abnormal opening in the bladder and the sphincter mechanism is intact. Given such data, the conclusion must be reached that urine must be coming from some point above the bladder and emptying at some point below the sphincter and that is exactly what occurs in some cases of ectopic vaginal ureter. In adding another case of this type to the few which have been reported, Deming² has reviewed the literature and gives a crisp analysis of this unusual condition. It must be recalled that the ureter develops from the Wolffian duct, that the vestibule also develops from the same source, but that the vagina is of Muellierian origin. This may explain why so

many ectopic ureters empty in the vestibule since both have the same origin. The most logical theory for the supernumerary vaginal opening is based on the fact that instead of a single invagination from the Wolffian duct, there are two or more anlagen, each forming a ureter with separate implantation into the kidney. As the Wolffian duct shifts downward with the urogenital sinus, it carries the upper ureter with it and causes a lower implantation of the upper ureter. If the two ureteral buds develop at the same time, their bladder openings may be near together, but if the upper ureter develops later, it may be carried below the bladder by the Muellerian duct to empty into the genital tract, as in the vagina. The vaginal opening of these ectopic ureters is practically always on the anterior wall in the midline, although nearer the cervix the opening may be more lateral. The symptoms of an ectopic vaginal ureter are quite definite. All of the cases have vaginal dripping of urine day and night, but in addition there are normal urinations from the urethra since the other ureter or ureters open into the bladder. If the ectopic ureter becomes infected there will be purulent urine coming from the vagina. In 4 cases reported the symptoms from infection, such as pain and elevation of temperature, overshadowed the urinary picture to such an extent that the patients were operated upon for appendicitis or renal suppuration. The kidney attached to an ectopic ureter is of little functional value and is prone to infection. Therefore no attempt should be made to conserve these kidneys and ureters. Heminephrectomy may be done if vessels are distinct to each kidney. If infection has not occurred, total ureterectomy offers an easy method of treatment; but once the kidney or ureter becomes infected, complete nephro-ureterectomy is indicated.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 20, 1942

Trichomonas Vaginalis in Tissue Cultures and Their Effect on Tissue Culture Cells. M. J. HOGUE (Department of Anatomy, Univ. of Penna.). Dr. Trussell's bacteria-free strain of *Trichomonas vaginalis* was introduced into human fetal and chick embryonic tissue cultures.

Its behavior in the tissue culture cells was recorded by moving film. The trichomonas swarmed about the explanted tissue and swam freely over the fibroblasts, epithelial cells and sympathetic nerves. They attached themselves by their axostyles to nerves and cells and whirled about. They entered the lumen of pieces of chick embryo intestine. No mechanical injury to the cells was observed. They formed rosettes which rolled over the tissue cultures. They pushed and pulled about masses of plasma granules. They often sent out a proboscis-like structure while feeding over the tissue cultures.

T. vaginalis is very injurious to tissue culture cells. When a rich culture was added to a tissue culture, the cells soon drew in their processes, the nuclear membrane and nucleolus became distinct and the cytoplasm granular. The cells were dead in 4 to 5 hours, though the trichomonas lived for several days. Controls were made for all experiments and the tissue cultures grew well in the same medium in which the trichomonas lived.

Filtrates of old cultures of trichomonas were added to tissue cultures and caused the same effect as the living trichomonas.

Cultures of trichomonas heated at 56° F. for 15 and 30 minutes and at 60° F. for 20 minutes caused the death of tissue culture cells. It was a slower process with occasional recovery of the tissue cultures.

Metts tubes and Gillman and Cowgill's test were used to determine the presence of a proteolytic enzyme. Both gave negative results.

Cytochrome *c* Content, Nucleic Acid Phosphorus, and Oxidation Rate of Epithelial Tissues and Neoplasms. OTTO ROSENTHAL and DAVID L. DRABKIN (Harrison Department of Surgical Research and Department of Physiological Chemistry, Univ. of Penna.). A micro-spectrophotometric technique has been developed for the determination of ferrocytochrome *c*. This has permitted the determination of this pigment isolated from smaller amounts of tissue than hitherto possible when utilizing direct methods of analysis. Upon the same tissues nucleic acid phosphorus (protein-bound phosphorus) has been determined and used as an index of cellularity. The oxidation rates of both succinate and p-phenylenediamine by the same tissues were determined by means of the usual manometric technique. The epithelial tissues studied included kidney cortex, liver, brain, submaxillary gland, gastric and colon mucosa, and lung. Data were gathered upon three species—rat, rabbit and man.

The data have permitted correlation of interest to be drawn, and have led to a new view of the problem of carcinogenesis.

1. The cytochrome *c* content and the oxidation rate of certain epithelial tissues—gastric mucosa and lung—are low. Kidney cortex, which has a high cytochrome *c* content and high oxidation rate, was used as the standard of comparison.

2. The cytochrome *c* content of tissues in the different species is an inverse function of body size. All tissues of man show a relatively low content of cytochrome *c* in comparison with the corresponding tissues of smaller animals. This appears to be a new finding.

3. The cytochrome *c* content and oxidation rate of neoplastic tissues (gastric and colon mucosa) are of the same order of magnitude as that of the parent epithelial tissues from which the tumors arise.

These findings correlate well with the frequent incidence of neoplasms in man and in mucous epithelium. They suggest that epithelial tissues whose aërobic metabolism is low are those in which neoplasms most frequently arise. It is probable that in such tissues the transition from an aërobic to a relatively anaërobic metabolism—characteristic of malignant tissue—occurs more readily than in epithelial tissues high in cytochrome *c* and with high aërobic metabolism.

The Effect of Therapeutic Blood Levels of Sulfonamides Upon Wound Healing. H. A. ZINTEL, D. B. FRESHWATER, J. D. HARDY, W. M. HARRIS, JR., C. S. NEER, 2D, and S. W. ROBINSON (Harrison Department of Surgical Research, Univ. of Penna.). The extensive use of sulfonamides in the prevention and treatment of surgical infections has led to the question of the possible effect of these drugs upon the uninfected wound. Because of differences of opinion in previously reported work, we undertook to test the tensile strength and to study sections of histologic wounds of the skin, fascia and stomach wall of dogs which were given sulfanilamide and sulfadiazine by stomach tube. High blood levels of these drugs were maintained throughout the experiment. The wounds were tested at intervals between the third and thirteenth postoperative days. The tensile strength of the skin and fascia was tested by means of a tensiometer, while that of the stomach was tested by the air inflation method.

No appreciable differences were noted between the tensile strengths of skin, fascia and stomach wall of the sulfadiazine-treated, the sulfanilamide-treated and the control animals. The histologic sections of the experimental animals were identical to those of the control group. There were no evidences of inflammatory reaction, edema nor hematomata. We may conclude, therefore, that within the limitations covered by these experiments sulfanilamide and sulfadiazine may be administered orally in therapeutic doses without danger of prolonging the time of wound healing, or decreasing the tensile strength of the wounds, or in any way jeopardizing the cosmetic result.

Studies on the Nature of the Viruses of Influenzas A and B. LESLIE A. CHAMBERS, WERNER HENLE and ELIZABETH DUDLEY (Johnson Research Foundation, Univ. of Penna., and the Children's Hospital of Philadelphia). The virus of influenza A can be removed from the allantoic fluid of infected chick embryos by differential ultracentrifugation, and recovered in association with a protein fraction which is essentially homogeneous with respect to particle size as indicated by electron microscopy and by determination of the sedimentation velocity.

Approximately 1 gm. each of the virus proteins of influenzas A and B was collected, dried and used as material for determination of physical properties and chemical composition. It was found that the two proteins do not differ significantly in ultraviolet absorption, specific volume, mass, shape, or in content of arginine, tryptophane, tyrosine, total nitrogen, protein nitrogen, purine nitrogen, phosphorus and ash. Both contain d-ribose but no desoxyribose was detected. On the other hand, the two viruses were found to differ significantly in content and distribu-

tion of sulfur especially with respect to cystine. The contents of cystine (including cysteine) in viruses A and B were 4.3% and 3.4% respectively. Methionine was present in essentially equal quantities (1.7%) in the 2 cases, while inorganic sulfur was present in negligible amounts. In a broad sense the properties suggest those of the plant viruses whose properties have been determined.

When subjected to low temperatures the virus particles aggregate in a regular manner resulting in the formation of crystalline aggregates. Solution of the crystals is readily accomplished by moderate heating or by dilution. The sequence of formation of crystals from the virus proteins has been followed by electron microscopy.

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RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal of the American Medical Association* with its large circulation, will also emphasize the point.

We should like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, i.e., that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" gives the more exact meaning.

THE EDITOR.

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